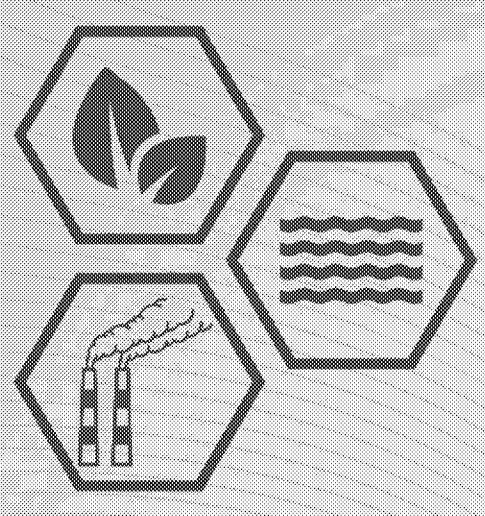
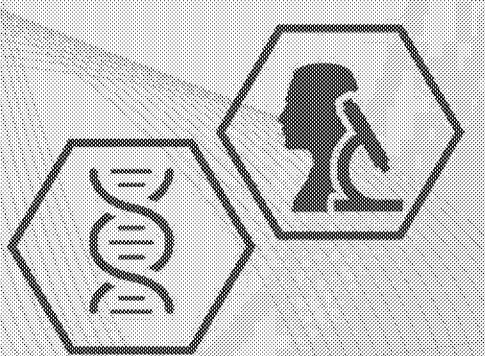


Toxicological Profile for Lead

Draft for Public Comment

September 2018



ATSDR
U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30329-4027

Physical Mailing Address:
4770 Buford Highway
Building 102, 1st floor, MS F-57
Chamblee, Georgia 30341

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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

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VERSION HISTORY

Date	Description
DATE PENDING	Draft for public comment toxicological profile released
August 2007	Final toxicological profile released
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CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Henry Abadin, M.S.P.H. (Lead)
Jessilynn Taylor, M.S., CDR USPHS
Melanie Buser, M.P.H.
Franco Scinicariello, M.D., M.P.H.
Jennifer Przybyla, Ph.D.

ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Julie M. Klotzbach, Ph.D.
Gary L. Diamond, Ph.D.
Lara L. Chappell, Ph.D.
Laura A. McIlroy, B.A.

SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:
Includes ATSDR; National Center for Environmental Health (NCEH); National Institute of Occupational Health and Safety (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:
ATSDR, Division of Community Health Investigations; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice; Occupational Safety and Health Administration (OSHA); Department of Defense (DoD).

PEER REVIEWERS

1. Howard Hu, M.D., M.P.H., Sc.D., Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan

2. Anthony Knafla, M.Sc., DABT, P. Biol., Founder/Senior Scientist & Manager, Equilibrium Environmental Inc., Calgary, Canada

3. Nelly Mañay, Ph.D., Professor, Department of Toxicology and Environmental Hygiene, Faculty of Chemistry, University of the Republic of Uruguay, Montevideo, Uruguay

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Lead (Pb) is an element that is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world. A major source of Pb in the U.S. environment has historically been anthropogenic emissions to the atmosphere from combustion of leaded gasoline, which was phased out of use after 1973 and then banned in 1995 (with the exception of fuels for piston-driven aircraft) (EPA 1996a). Lead continued to be used as an anti-knock agent in National Association for Stock Car Auto Racing (NASCAR) fuels until it was phased out beginning in 2008. Deteriorating Pb-based paints from weathered surfaces (which produce highly concentrated Pb debris and dusts) in older housing stock (pre-1978) continues to be a source of childhood Pb poisoning in the United States (CDC 1991, 2012d). The combination of corrosive water and Pb pipes or Pb-soldered joints in either the distribution system or individual houses can create localized zones of high Pb water concentrations (EPA 1989d, 2007a; Hanna-Attisha et al. 2016). Other anthropogenic sources of Pb have included mining and smelting of ore; manufacture of and use of Pb-containing products (e.g., Pb-based paints, pigments, and glazes; electrical shielding; plumbing; storage batteries; solder; and welding fluxes); manufacture and application of Pb-containing pesticides; combustion of coal and oil; and waste incineration.

Pb does not degrade in the environment, although it can exist in various chemical forms. Particulate matter contaminated with Pb can be transported through air, water, and soil. In general, atmospheric deposition is the largest source of Pb found in soils not impacted by other local non-air sources (e.g., dust from deteriorating leaded paint). Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb. Pb adsorbs strongly to most soils, which limits the rate of leaching. Soil acidity (pH) and composition are the most important factors affecting solubility, mobility, and phytoavailability of Pb in soil. Other conditions that increase Pb mobility in soil are reducing conditions and high chloride content.

The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Pb has also been found in a variety of other consumer products including storage batteries, solders, pottery glazes, leaded crystal glassware, cosmetics, hair dyes, jewelry, gun shot and ammunition, relic fishing sinkers, tire weights, and imported children's toys, traditional or folk remedies, and candy/food packaging. For adults, exposure to levels of Pb beyond background is usually associated with occupational exposures. For children, exposure to high levels of Pb is associated with living in areas

contaminated by Pb (e.g., soil or indoor dust in older homes with Pb-based paint). The primary source of Pb exposure to children is from surface dusts (on the ground or entrained) that contain Pb from a variety of sources including deteriorated Pb-based paint (CDC 2009; Lanphear et al. 1998a; Succop et al. 1998). Environmental Pb is particularly accessible to children because of their more intensive hand-to-mouth activity and the proximity of the child breathing zone to Pb entrained from surface dusts. Because Pb is transported from soil very slowly, historic sources of deposition of Pb to soil continue to contribute to current exposures (Laidlaw and Filipelli 2008; Laidlaw et al. 2012).

Blood Pb (PbB) has been used as a biomarker of Pb exposure, and periodic surveys of PbB of the U.S. population are conducted by the Centers for Disease Control and Prevention (CDC). Based on data from the National Health and Nutrition Examination Survey (NHANES) (2015–2016, CDC 2018a), the geometric mean PbB in a representative sample of U.S. adults, ≥20 years old, was 0.920 μg/dL (95% confidence interval [CI] 0.862, 0.982). The geometric mean blood PbB of a representative sample of U.S. children, 1–5 years old, was 0.758 μg/dL (95% CI 0.675, 0.850). PbBs in the U.S. have decreased considerably in the last several decades as a result of removal of Pb from gasoline and restrictions placed on the use of Pb in residential paints (Brody et al. 1994; CDC 2011, 2018a; Pirkle et al. 1994, 1998; Schwartz and Pitcher 1989).

Seasonal variations in blood lead concentration (PbB) levels in children have been observed, with a general trend of increasing PbB during late summer and early fall (Gulson et al. 2008; Johnson and Bretsch 2002; Laidlaw et al. 2005). Seasonal patterns in behavior (e.g., outdoor activities) and weather that promotes re-entrainment and transport of dust Pb (humidity and wind velocity) may contribute to the observed seasonal patterns in PbB (Laidlaw et al. 2005, 2012) and provide additional evidence for surface dusts being a major contributor to child Pb exposure and PbB.

1.2 SUMMARY OF HEALTH EFFECTS

The toxicity of Pb to humans has been known for over 2,000 years, and is not disputed. Early epidemiological studies focused on overt toxicity associated with high occupational exposures. However, during the past few decades, there has been a growing awareness that low-level environmental exposure resulting in PbB <10 μg/dL is associated with adverse effects, particularly in children. As a result, U.S. public health policy has changed to focus on lowering PbB levels to well below 10 μg/dL. Therefore, the primary objective of current research is on health effects associated with PbB ≤10 μg/dL.

The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of evidence regarding health effects in humans. Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb. This potentially leaves out discussion of effects that may have been observed in animal models that have not been studied in humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics.

To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of μg/dL). Blood Pb concentration reflects both ongoing exposure and Pb stores in bone, which can be transferred to blood. Because of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months and not necessarily the larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI), which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct, noninvasive measurements of bone Pb concentrations have been used as a metric of long-term exposure on the basis that most of the absorbed Pb retained in the body will reside in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect are typically unknown or highly uncertain.

Adverse health effects of Pb have been observed in every organ system. This is because the mechanisms that induce toxicity are common to all cell types and because Pb is widely distributed throughout the body. Health effects of Pb have been observed in all organ systems over a wide PbB range (≤10–>50 μg/dL). Exposure thresholds for effects on specific organ systems have not been identified and it is not possible to determine from the epidemiological data which organ systems are the most sensitive

(i.e., primary) targets for Pb toxicity. It is also important to note that effects observed in adults, especially older adults, may be due to higher environmental or occupational exposures in the past; therefore, exposure history is an important consideration in epidemiological studies on the health effects of Pb.

The most extensively studied health outcomes, as described below, are neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects. Neurological effects of Pb are of greatest concern because effects are observed in infants and children and may result in life-long decrements in neurological function. Infants are born with a Pb burden derived from maternal transfer *in utero* and subsequently can continue to absorb maternal Pb from ingestion of breast milk. Children are also more vulnerable because of behaviors that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity) and because gastrointestinal absorption of ingested Pb is higher in children compared to adults, possibly due to a combination of physiological differences and differences in diet and nutrition. The following briefly summarizes health effects of chronic exposure to Pb observed in humans. More detailed information, including reference citations, is provided in Chapter 2.

Neurological Effects in Children. Numerous prospective and large cross-section studies in children provide consistent evidence of decrements in neurological function, including decrements in cognitive function (learning and memory), altered behavior and mood (attention, hyperactivity, impulsivity, irritably, delinquency), and altered neuromotor and neurosensory function (visual-motor integration, dexterity, postural sway, changes in hearing and visual thresholds). These effects have been associated with a PbB range from ≤10 to >50 μg/dL, with several studies providing evidence for effects at PbB ≤5 μg/dL. Taken together, studies support the concept that Pb affects cognitive function in children prenatally and/or environmentally exposed to low levels of Pb. No threshold for these effects has been identified. Decrements in cognitive function increase with PbB, and several PbB-effect models predict that larger decrements in cognitive function would occur when PbB increases from 1 to 10 μg/dL, compared to when PbB increases from levels >10 μg/dL. At higher PbB (>30 μg/dL), other neurotoxic effects have been observed, including alterations in nerve function (decrements in fine and gross motor skills, peripheral neuropathy) and encephalopathy.

Neurological Effects in Adults. Epidemiological studies in adults demonstrate decrements in neurological function associated with PbB. All of the cognitive and neurobehavioral effects of Pb observed in children also have been observed in adults associated with PbB ranging from ≤10 to >50 μg/dL, with evidence of effects occurring at PbB ≤5 μg/dL. At higher PbB (>30 μg/dL), other observed neurotoxic effects include peripheral neuropathy, psychiatric symptoms (depression, panic

disorders, anxiety, hostility, confusion, anger, and schizophrenia), and changes in regional brain volumes and neurochemistry. It is not clear if cognitive decrements are related to exposures that occurred during adulthood or during periods of nervous system development (e.g., prenatal and childhood exposures) or if effects are due to cumulative exposure. Results of a few studies that have followed children to early adulthood show an association between child PbB and behavioral and neuroanatomical changes in adults, suggesting a possible impact of exposures on childhood to adult outcomes.

Renal Effects. Adverse renal effects of Pb are well-established in numerous epidemiological studies. Studies show consistent evidence of renal damage and reduced renal function associated with a wide range of PbB (≤10–50 μg/dL), with several studies providing evidence for effects at PbB ≤5 μg/dL. Deficits in renal function include enzymuria, proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate (GFR). At higher PbB (>30 μg/dL), Pb-induced nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, interstitial fibrosis, and tubular necrosis. Note that Pb-induced decrements in renal function can lead to higher Pb body burden due to decreased excretion of Pb (i.e., reverse causality).

Cardiovascular Effects. A large number of epidemiological studies in adults show adverse cardiovascular effects associated with a PbB range from ≤10 to >50 μg/dL. Effects on blood pressure is the most-studied cardiovascular outcome, with studies showing increased systolic and diastolic blood pressure, with some evidence of effects occurring at PbB ≤5 μg/dL. A few studies show increased blood pressure in children and pregnant women. Nawrot et al. (2002) estimated that with doubling of PbB (for example, from 5 to 10 μg/dL), systolic and diastolic blood pressure would increase by 1 and 0.6 millimeters of mercury, respectively. Other cardiovascular effects include increased risk of hypertension and heart disease, atherosclerosis, altered cardiac conduction, cardiac disease, and increased mortality due to cardiovascular disease.

Hematological Effects. The toxicity of Pb to the hematological system of humans has been established in numerous studies in adults and children. Exposure to Pb causes dose-dependent decreases in heme synthesis through inhibition of the enzyme delta-aminolevulinic acid dehydratase (δ-ALAD). At PbB ≤10 μg/dL, decreased blood hemoglobin is observed; however, it should be noted that the magnitude of this decrease is typically small and may not represent a biologically significant change. As PbB increases, further decreases in blood hemoglobin and loss of erythrocytes due to a Pb-induced increased membrane fragility results in the development of anemia (NAS 2013). Other effects of Pb on the hematological system include decreased activity of other erythrocyte enzymes (pyrimidine

5'-nucleotidase or red blood cell membrane Ca^{2+}/Mg^{2+}ATPase) and altered levels of plasma erythropoietin (a hormone that stimulates red blood cell formation); however, fewer studies on these endpoints have been published and study results are mixed.

Immunological Effects. Epidemiological studies provide evidence that Pb exposure can perturb the immune systems of children and adults. Evidence for this derives from changes in various indicators of humoral and cell-mediated immunity in association with increasing PbB. Effects have been observed in populations that had average PbB <10 μg/dL. These effects are consistent with more extensive studies conducted in animal models and isolated immune cells that have shown that Pb can perturb the humoral and cell-mediated immune systems, leading to sensitization, autoimmunity, and inflammation (EPA 2014c; NAS 2013).

Reproductive Effects in Males. Health effects of Pb on the male reproductive system have been evaluated in numerous epidemiological studies. Effects include damage to sperm (decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm), possible alterations in serum levels of reproductive hormones (testosterone, estradiol, luteinizing hormone [LH], and follicle-stimulating hormone [FSH]), decreased fertility, and histopathological changes to the testes. Severity of these effects increases with PbB. Studies conducted in populations with mean PbB ≤10 μg/dL provide evidence of damage to sperm, although effects are more consistently observed at PbB >10 μg/dL. Regarding effects on serum levels of reproductive hormones, results of available studies for PbB ranging from ≤10 to >50 μg/dL are inconsistent; thus, Pb-induced effects on circulating reproductive hormones are not firmly established. At higher PbB (>10 μg/dL), a few studies provide evidence of more severe effects, including decreased fertility and histopathological damage to testes.

Reproductive Effects in Females. Compared to studies of male reproductive effects, the epidemiologic literature database for effects of Pb on the female reproductive system is smaller, with most epidemiological studies conducted in populations with mean PbB ≤10 μg/dL. Studies provide some evidence of alterations in serum reproductive hormone levels (estradiol, LH, and FSH), decreased fertility, increased spontaneous abortion, increased preterm birth, and decreased age at onset of menopause. However, results are inconsistent, with several studies reporting no association between PbB and female reproductive effects.

Developmental Effects (Excluding Neurodevelopmental). Numerous epidemiological studies have evaluated developmental outcomes, with most studies conducted in populations with maternal and/or umbilical cord PbB ≤10 μg/dL. Some studies provide evidence of decreased birth size (weight, length, head circumference), decreased child growth (weight, height, head circumference, trunk length, leg length, arm length, body mass index [BMI]), and delayed onset of puberty in males and females. Although it is difficult to assess dose-dependence for developmental effects within the relatively narrow range of PbB (≤10 μg/dL) in most studies, dose-related decreases in birth weight have been observed in populations with PbB ≤10 μg/dL. Although studies provide evidence of associations between PbB and developmental outcomes, results are inconsistent and several studies, including prospective studies, show no associations with non-neurodevelopmental outcomes.

Other Health Effects Associated with Pb. In addition to the effects summarized above, health effects to other organ systems have been reported. The epidemiological databases for these effects are much less extensive than for the effects reviewed above. Effects described below occur over a wide range of PbBs, including PbB ≤10 μg/dL. However, results are inconsistent and insufficient data are available to provide information on dose-response relationships.

- ***Respiratory Effects.*** Associations have been observed between PbB and decreased lung function, increased bronchial hyperreactivity, symptoms of respiratory disease, and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease).
- ***Endocrine Effects (Excluding Reproductive Hormones).*** Studies in adults, adolescents, and children show effects on thyroid function, cortisol levels, vitamin D levels, and serum levels of growth factors. Effects on thyroid function are the most studied effect, although results do not demonstrate a consistent pattern of effect.
- ***Hepatic Effects.*** Most studies were conducted in workers with PbB >10 μg/dL. Several studies show altered plasma levels of liver enzymes, although no consistent pattern of effects has been observed. Liver enlargement and increased gall bladder wall thickness have been associated with PbB.
- ***Musculoskeletal Effects.*** Studies provide evidence of bone loss, increased markers of bone metabolism/turn over, and adverse periodontal and dental effects (periodontal bone loss, tooth loss, periodontal disease, dental caries) in adults and children.
- ***Gastrointestinal Effects.*** Gastrointestinal colic is a predominant clinical symptom of Pb poisoning. Epidemiological studies provide evidence of gastrointestinal symptoms (abdominal

colic/pain, nausea, vomiting, diarrhea, and/or constipation) associated with PbB ranging from 8 µg/dL to approximately 100 µg/dL.

- ***Body Weight Effects.*** A few studies evaluating effects of PbB ≤10 µg/dL on body weight provide some evidence of decreased body weight in children and adults, although inconsistent results have been reported.
- ***Ocular Effects (Excluding Neurological Effects).*** Limited data provide some evidence that exposure to Pb is associated with macular degeneration in adults and increased risk of cataracts.

Cancer. Numerous epidemiological studies have evaluated associations between Pb exposure and cancer. Although studies provide limited evidence of carcinogenicity of Pb in humans, results are inconsistent, with several negative studies, and interpretation of data may be limited due to confounding factors (e.g., smoking status, family history of cancer, co-exposure to other carcinogens). At PbB ≤10 µg/dL, increased risks were reported for all cancers and lung cancer. At PbB >10 µg/dL, increased risks were observed for all cancer, respiratory tract cancer, stomach cancer, intestinal cancer, cancer of the larynx, and glioma.

The Department of Health and Human Services classified Pb and Pb compounds as reasonably anticipated to be human carcinogens (NTP 2016). EPA has classified Pb as a probable human carcinogen based on sufficient evidence in animals; evidence in humans was considered inadequate (IRIS 2004). The International Agency for Research on Cancer (IARC) has classified inorganic Pb compounds as probably carcinogenic to humans (Group 2A) based on sufficient evidence in animals and limited evidence in humans; evidence for organic Pb compounds was considered to be inadequate in humans and animals (IARC 2006).

1.3 MINIMAL RISK LEVELS (MRLs)

As reviewed in Section 1.2, epidemiological studies have evaluated the health effects of Pb in all organ systems. For the most studied endpoints (neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental), effects occur at the lowest PbBs studied (≤5 µg/dL). Because clear thresholds for these effects have not been identified, MRLs for Pb have not been derived.

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of lead (Pb). It contains descriptions and evaluations of epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect.

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of epidemiology studies included in this chapter of the profile.

Since development of the 2007 Toxicological Profile on Lead (ATSDR 2007), results of numerous epidemiological studies have prompted growing attention to the adverse health effects of Pb exposures that result in blood Pb concentrations (PbB) of <10 μg/dL (EPA 2014c). Awareness of the potential adverse consequences of such exposures has led to changes in U.S. public health policy, with a focus on lowering PbB levels to well below 10 μg/dL (CDC 2012d; EPA 2016b). In 2012, CDC established a PbB reference value for lead, replacing the 10 μg/dL level of concern. The reference value is based on the 97.5th percentile of the PbB distribution among children 1–5 years of age in the United States, using data generated by the National Health and Nutrition Survey (NHANES) (CDC 2012d). At that time, the PbB reference was approximately 5 μg/dL (NHANES 2011–2012) (CDC 2018a). The reference value would be updated every 4 years using the two most recent NHANES surveys and would be used in recommendations for follow-up evaluations and identification of high-risk childhood populations (CDC 2012d). It is likely that PbB values will continue to decline; therefore, the primary focus of this toxicological profile is on health effects associated with low Pb exposure (i.e., those observed at PbB ≤10 μg/dL). Information on health effects observed over a wide PbB range (≤10 to >50 μg/dL) is also included to present an overview of exposure-response relationships.

Literature Search Strategy. The literature on health effects of Pb in humans is enormous, with countless epidemiological studies in workers and the general population, including children. Due to the extent of the Pb database in humans, it is impossible to cite all, or even most, of the studies on health effects of Pb; thus, this profile does not attempt to provide a comprehensive review of all literature; instead, the profile summarizes the major lines of epidemiological evidence regarding health effects in humans. Although the literature database on adverse effects of Pb in laboratory animals is also extensive, given the large number of studies available in humans, animal studies are not included in this toxicological profile. For a recent review of studies in animal models, the reader should consult the EPA's Integrated Science Assessment for Lead (EPA 2014c).

The following were used as primary sources to identify literature on health effects of Pb:

- The previous Toxicological Profile for Lead (ATSDR 2007) was used to identify literature published through 2007.
- The EPA (2014c) Integrated Science Assessment for Lead was used to identify literature published from 2006 to 2013.
- Literature searches were conducted from 2013 to 2016 to identify studies published after EPA (2014c).

In addition, recent reviews by NTP (2012) and NAS (2013) were consulted. As anticipated, the literature search revealed an extensive epidemiological database of literature published since 2013. To narrow the evaluation to those studies of greatest utility identifying health effects of low exposures to Pb exposure, a series of inclusion criteria were defined; only studies meeting the criteria were considered for inclusion in the toxicological profile. These criteria are described further in Appendix B. Data from selected studies were tabulated and discussed in subsequent sections of this chapter.

Duration of Exposure. Typically, toxicological profiles organize the discussion of health effects according to exposure duration categories. However, this is not a particularly informative approach to the discussion of Pb epidemiology. The epidemiologic study of Pb toxicity in human populations has relied on internal dose metrics (PbB, bone Pb) for evaluating associations between health outcomes. These metrics are considered to represent relatively recent exposure history, in the case of PbB, and longer-term cumulative exposure, in the case of CBLI or bone Pb. However, neither metric offers a confident estimate of exposure duration or of changes in lead exposure over time (including peak exposure periods that may have occurred in the past), and, in general, the complete exposure history is not known. Health

outcomes associated with acute exposures is available from clinical cases studies of Pb poisoning (see Section 2.2). However, even in these cases, the exposure duration that proceeded the identification of the case is rarely known with certainty.

Routes of Exposure. For the general population, exposure to Pb occurs primarily via the oral route, with some contribution from the inhalation route, whereas inhalation exposures can be more important in occupational settings, depending on particle size. In addition, occupational exposure to organic Pb compounds may involve dermal absorption as a significant exposure route. This profile does not attempt to separate health effects by route of exposure. As noted previously, epidemiology studies have relied on internal dose metrics (PbB, bone Pb), which reflect Pb body burden (to varying degrees), irrespective of the route of exposure. The primary systemic toxic effects of Pb are the same regardless of the route of entry into the body,

Exposure Metric. To quantify exposure in humans, data are expressed in terms of absorbed Pb, and not in terms of external exposure levels (e.g., concentration in water) or dose (e.g., mg/kg/day). The most common metric of absorbed dose for Pb is the concentration of lead in blood (PbB), although other measures of exposure (e.g., concentration of Pb in bone, hair, teeth, or urine) are used; however, measurements of Pb in urine, teeth, and hair are not as reliable as measurements in blood or bone. PbB mainly reflects exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of Pb in bone (see Section 3.1). Pb in bone is considered a biomarker of cumulative or long-term exposure because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Most of the body burden of Pb (the total amount of Pb in the body) is distributed to the bone, with approximately 94 and 76% of the body burden found in bone in adults and children, respectively. The remainder is distributed to blood and soft tissues. However, the concentration of Pb in blood can vary considerably with age and physiology/lifestage (e.g., pregnancy, lactation, menopause). For this reason, measurement of Pb in bone has seen wider application in epidemiological studies of adults in which measures of cumulative lifetime exposures are of interest. However, bone Pb measurements require specialized radiologic equipment (e.g., K-shell x-ray fluorescence; XRF) and, as a result, are used less commonly than PbB in human epidemiology. Since most of the epidemiology has relied on PbB as the dose metric, this profile has focused on describing dose-response relationships based on PbB to facilitate comparisons across studies and endpoints. This approach also aligns with public health practices, which rely on PbB for evaluating elevated exposures to Pb (CDC 2012d; EPA 2016b). However, it is recognized that some health outcomes may be correlated with cumulative exposure, in which case, bone Pb may be a better dose metric than PbB. For these

outcomes, short-term variation in PbB may contribute to exposure classification error (i.e., the same PbB could be observed in individuals who have different bone Pb). The exposure history of the subjects may also be an important factor in determining associations observed between outcomes and blood or bone Pb. Some studies of historically exposed occupational populations (e.g., former workers) have found stronger associations between bone Pb and health outcomes than with PbB, while some studies of concurrently exposed populations have found stronger associations with PbB (Shih et al. 2007).

Overview of Health Effects of Pb. The health effects of Pb are diverse, and exposure to Pb is associated with toxicity to every organ system. This is not surprising because the mechanisms of action associated with Pb-induced toxicity, including perturbations of ion homeostasis and transport, protein binding, oxidative stress, and inflammation, are common to all cell types. In addition, Pb is widely distributed throughout the body, and has been measured in all tissues evaluated (see Section 3.1.2). For all organ systems, toxicity has been observed at PbB $\leq$10 μg/dL. Even with the extensive amount of epidemiological data, no thresholds for effects in any organ system have been identified; therefore, it is not possible to determine from the epidemiological data which organ system is the most sensitive to effects of Pb exposure. Neurological effects of Pb are of greatest concern because effects are observed in infants and children; furthermore, these effects may result in life-long decrements in neurological function. Children are also more vulnerable because of behaviors that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity) and because gastrointestinal absorption of ingested Pb is higher in children compared to adults, possibly due to a combination of physiological differences and differences in diet and nutrition. The weight-of-evidence for all adverse health effects is strongly supported by studies in animal models and *in vitro* systems; see EPA (2014c) for a review of this literature.

Effects observed in association with PbB are briefly described below. Note that for some of the effects listed below, study results are not consistent, which limits interpretation of observations; this is reviewed in more detail in subsequent sections for each organ system in Chapter 2. The most extensive epidemiological databases examining Pb are for neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects.

- **Neurological Effects:**
    - **Children.** Decreased cognitive function; altered mood and behaviors that may contribute to learning deficits, altered neuromotor and neurosensory function, peripheral neuropathy, and encephalopathy.

  - **Adults.** Decreased cognitive function including attention, memory, and learning; altered neuromotor and neurosensory function; altered mood and behavior; and decreased peripheral nerve conduction velocity.

- **Renal Effects.** Decreased GFR, proteinuria, enzymuria, impaired tubular transport, and histopathological damage.

- **Cardiovascular Effects.** Increased systolic and diastolic blood pressure, increased risk of hypertension, atherosclerosis, altered cardiac conduction, increased risk of heart disease, and increased mortality due to cardiovascular disease.

- **Hematological Effects.** Inhibition of δ-ALAD leading to decreased blood hemoglobin and anemia, decreased activity of other erythrocyte enzymes, and altered plasma erythropoietin (EPO) levels.

- **Immunological Effects.** Perturbation of humoral and cell-mediated immune systems, decreased resistance to disease, sensitization, autoimmunity, and inflammation.

- **Reproductive Effects:**
  - **Males.** Effects on sperm, alterations in semen quality, decreased fertility, histopathological damage to the testes, and possible altered serum concentrations of reproductive hormones.
  - **Females.** Possible alterations in serum concentrations of reproductive hormones, decreased fertility, spontaneous abortion, preterm birth, and decreased age at the onset of menopause.

- **Developmental Effects.** Decreased birth weight and size, decreased anthropometric measures in children, and delayed onset of puberty in males and females.

Other health outcomes associated with PbB include the following:

- **Respiratory Effects.** Decreased lung function, increased bronchial hyperreactivity, increased risk of asthma, and obstructive lung disease.

- **Hepatic Effects.** Possible increases in plasma liver enzymes and cholesterol, enlarged liver, and increased thickness of gall bladder wall.

- **Endocrine Effects.** Possible alterations in serum of thyroid hormones, altered cortisol responses, alteration in serum growth factors, and decreased serum vitamin D levels.

- **Gastrointestinal Effects.** Abdominal pain/colic, nausea, vomiting, and diarrhea and/or constipation.

- **Musculoskeletal Effects.** Bone loss, osteoporosis, dental caries, tooth loss, and periodontitis.

- **Ocular Effects.** Possible macular degeneration and cataracts.

- **Cancer.** Increased risk of cancer, including all cancers, cancer of the respiratory tract, intestinal tract, and larynx, and glioma.

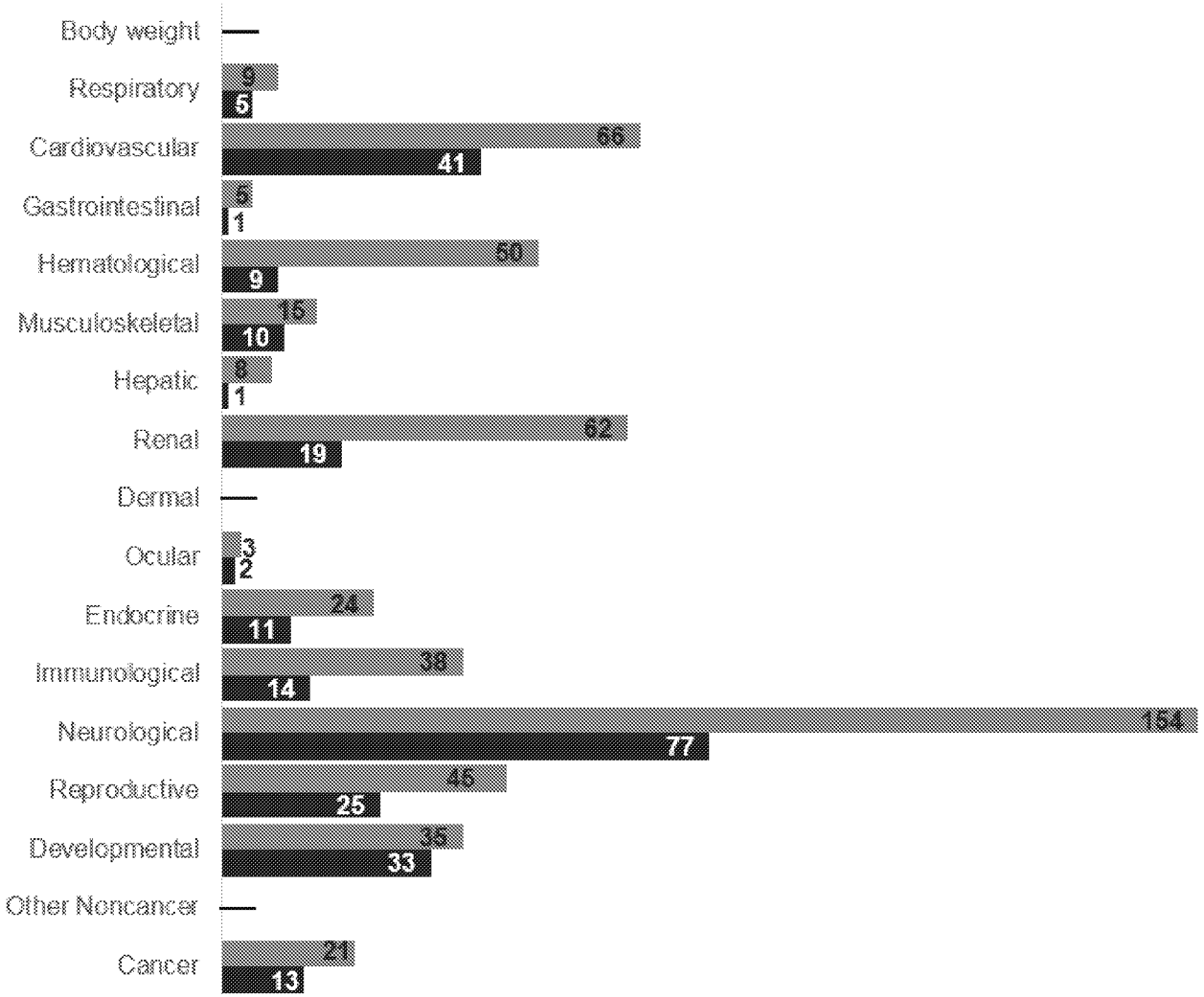
Many specific health effect endpoints have been evaluated in numerous studies. To provide the reader with a weight-of-evidence for these endpoints, the profile indicates if results are consistent and corroborated in numerous studies or if results are inconsistent (or mixed).

Figure 2-1 shows the numbers of epidemiological studies included in this chapter of the toxicological profile, based on health outcome studied. The number of studies evaluating effects at PbB $\leq$10 μg/dL also is indicated. As noted above, due to the enormous number of epidemiological studies published, the profile does not attempt to provide a comprehensive review of all literature. Therefore, this figure should not be interpreted as depicting all epidemiological studies that have been published on Pb toxicity.

Figure 2-1. Overview of the Number of Studies Examining Associations Between PbB and Health Effects[a]

Most studies examined the potential cardiovascular, renal, and neurological effects of lead

A subset of studies evaluating health effects for **PbB ≤10 µg/dL** compared to **all PbB studies** (counts represent studies examining endpoint)



[a]Includes studies discussed in Chapter 2. A total of 540 epidemiological studies (including those finding no effect) have examined toxicity; some studies examined multiple endpoints.

2.2 ACUTE LEAD TOXICITY

Overview. No controlled studies in humans have evaluated the acute toxicity of Pb (acute Pb poisoning). Available information is anecdotal, obtained from numerous case reports. Thus, data are not sufficient to establish a dose-response relationship for acute toxicity relative to PbB. Acute Pb toxicity is characterized by symptoms of abdominal pain/colic, vomiting, constipation, peripheral neuropathy, and cerebral edema and encephalopathy, which can lead to seizures, coma, and death. Children are more susceptible than adults to acute Pb poisoning. Additional information on toxicity of ingested Pb debris (e.g., Pb shot) is provided in Appendix C.

Rather than reviewing numerous case reports, the information presented below was taken from the following reviews: Beers et al. (1999); Chisolm (1977); Klaassen (2001); Landrigan (1995); NAS (1972a); Needleman (2004); and Skerfving and Bergdahl (2015). Citations are only specifically noted below if quantitative information is discussed.

Confounding Factors and Uncertainties. There are several uncertainties from case reports on acute toxicity of Pb. Therefore, it is difficult to establish dose-response relationships for acute toxicity relative to PbB. Uncertainties include:

- Baseline PbB data are rarely available.
- There is a lack of quantitative data on the dose of Pb ingested.
- No information on the fractional absorption of ingested Pb.
- Time from ingestion of Pb to development of symptoms of acute Pb toxicity is often unknown.
- Time from ingestion of Pb to first clinical evaluation and PbB assessment is often unknown.
- Gastrointestinal symptoms and general malaise are typically the first symptoms of acute Pb toxicity to appear; these general symptoms are often attributed to other causes, leading to an initial misdiagnosis or delay in diagnosis.
- Data to develop PbB time-concentration curves are incomplete.
- Numerous factors may contribute to individual susceptibility to acute Pb exposure, including age, intercurrent illness, underlying developmental issues, dietary and nutritional status, concurrent medication use, and exposure to other chemicals.

Clinical Presentation of Acute Pb Toxicity. The onset of acute toxicity is rapid, usually occurring within 1–5 days of exposure. The main organ systems involved are the gastrointestinal, hematological, and

neurological systems. Signs and symptoms increase in severity with increasing PbB, ranging from mild to severe. Gastrointestinal effects include abdominal colic/pain, nausea, vomiting, diarrhea, and constipation. Massive loss of gastrointestinal fluids can lead to dehydration. Hematological effects include decreased hemoglobin synthesis, anemia, and acute hemolytic crisis characterized by anemia and hemoglobinuria. Numerous neurological symptoms are associated with acute Pb toxicity, including headache, hyperirritability, decreased activity, paresthesia, muscle pain and weakness, ataxic gait, decreased consciousness, cerebral edema leading to seizures and coma, encephalopathy, and death. Other reported symptoms include astringency of the mouth, metallic taste in the mouth, and thirst.

Susceptibility of Children. Children are more susceptible than adults to Pb poisoning because the fractional absorption of ingested Pb is higher than in adults and the developing central nervous system is more vulnerable to toxicity compared to a fully developed nervous system (Needleman 2004). In addition to being more sensitive than adults, acute toxicity in children may have long-lasting effects. For example, children who recover from acute encephalopathy can have long-term decreases in cognitive abilities, attention deficits, and impaired behavior. Children are also susceptible due to increased exposure.

Dose-Response Relationship for Acute Toxicity Relative to PbB. As noted above, data from case reports are not sufficient to establish a dose-response relationship for acute toxicity relative to PbB. Some general observations can be made from available reports; however, dose-response relationships are highly uncertain and may not apply to individuals acutely exposed to Pb. At PbB <30 μg/dL, signs and symptoms of acute toxicity typically are not observed. This should not be interpreted to mean that no Pb-induced adverse effects (e.g., decreased hemoglobin synthesis) occur at PbB <30 μg/dL, but that symptoms causing individuals to seek medical intervention (e.g., abdominal colic and vomiting) typically are not observed at PbB <30 μg/dL. As PbBs increase to >30 μg/dL, signs and symptoms of gastrointestinal and neurological toxicity are observed, with severity increasing with PbB. Pb-induced encephalopathy has been reported at PbB <100 μg/dL, but is more commonly associated with PbB >100 μg/dL (NAS 1972b). In a review of 96 cases of death due to acute Pb poisoning in children, death occurred at PbB >100 μg/dL (NAS 1972b).

2.3 DEATH

Overview. Numerous epidemiological studies have investigated associations between Pb exposure and death. Studies include exposure of workers and general populations, and report a wide range of PbB levels. In the general population, studies have shown significant associations between PbB and mortality

due to disease of blood and blood-forming organs. In occupationally exposed individuals, mortality due to infection, endocrine diseases, and digestive diseases were associated with PbB in male workers, but not female workers, while mortality due to respiratory disease was associated with PbB in a cohort of male workers. In addition, studies of the general population and Pb occupations show an association between PbB and cumulative "all-cause" mortality (including cancer). However, results are inconsistent and interpretation may be limited due to confounding factors. Studies assessing associations between PbB and mortality due to cardiovascular diseases and cancer are discussed in Sections 2.5 and 2.19, respectively, and are not reviewed here.

The following causes of death have been associated with PbB:

- ≤10 μg/dL:
  - Increased risk of death from all causes (including cancer and cardiovascular disease); evaluated in a few studies with generally consistent results.
- >10 μg/dL:
  - Increased risk of death from all causes (including cancer and cardiovascular disease); evaluated in several studies with positive associations in some studies.
  - Increased risk of death from chronic or unspecific nephritis or non-malignant kidney disease; evaluated in several studies with positive associations in some studies.
  - Increase risk of death from infection; demonstrated in one study.
  - Increased risk of death from endocrine disease; demonstrated in one study.
  - Increased risk of death from digestive disease; evaluated in several studies with positive associations in some studies.
  - Increased risk of death from diseases of the blood and blood forming organs; demonstrated in one study.
  - Increased risk of death from respiratory diseases (emphysema, pneumonia, and other respiratory diseases); evaluated in several studies with positive associations in some studies.

Confounding Factors. Numerous confounding factors can influence results of epidemiological studies evaluating associations between Pb exposure and mortality, including age, sex, BMI, ethnicity, poverty level, education, alcohol consumption, smoking status, hypertension, diabetes, family history of diseases, activity level, total cholesterol, postmenopausal status, nutritional status, and co-exposure with other metals (i.e., arsenic or cadmium).

Measures of Exposure. Studies examining the association between Pb exposure and mortality evaluate exposure by measurement of PbB.

Characterization of Effects. Numerous epidemiological studies have assessed associations between PbB and mortality. Studies of general populations and workers are briefly summarized in Table 2-1. In the general population, at PbB ≤10 μg/dL, a positive dose-response relationship was suggested for all-cause mortality and mortality due to coronary heart disease (Khalil et al. 2009, 2010; Menke et al. 2006; Schober et al. 2006), although Weisskopf et al. (2009) did not show an increased risk for all-cause mortality. At >10 μg/dL, results of occupational exposure and general population studies are mixed and do not establish a pattern of effects or exposure-response relationships. In the general population, findings of the Lustberg and Silbergeld (2002) study suggested dose-response for PbB and all-cause mortality. In Pb workers, a dose-effect relationship was observed for all-cause mortality and mortality due to endocrine disease, infection, and digestive disease (Chowdhury et al. 2014; Kim et al. 2015), although Malcolm and Barnett (1982) did not observe a dose-effect relationship between Pb and all-cause mortality in Pb battery workers.

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
PbB ≤10 µg/dL			
Cheung et al. 2013 Cross-sectional study; n=3,482 (NHANES III)	Mean (SE): 4.44 (0.14)	All-cause mortality[c]	**OR: 1.045 (1.013 1.079)***
Khalil et al. 2009, 2010 Prospective cohort study; n=533 women (age 65–87 years)	Quintiles • Q1: <4 • Q2: 4 • Q3: 5 • Q4: 6–7 • Q5: >7	All-cause mortality[c]	HR Q1 (reference) HR Q2: 0.80 (0.45,1.42) HR Q3: 0.70 (0.39, 1.24) HR Q4: 0.60 (0.34, 1.06) HR Q5: 1.20 (0.69, 2.09) **p-trend=0.905***
Khalil et al. 2009 Prospective cohort study; n=533 women (age 65–87 years)	Mean: 5.3 <8 (n=453) ≥8 (n=79)	All-cause mortality[c]	**Adjusted HR ≥8 µg/dL: 1.59 (1.02, 2.49); p=0.041***
		All-cause mortality excluding deaths due to cancer and cardiovascular disease	Adjusted HR ≥8 µg/dL: 1.22 (0.48, 3.10); p=0.673
Menke et al. 2006 Longitudinal study; n=13,946 (NHANES 1988–1994; mean age 44.4 years)	Mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.62	All-cause mortality[c]	Adjusted HR T1 (reference) T2: 0.91 (0.72, 1.15) **T3: 1.25 (1.04, 1.51)*** **p-trend=0.002***
Neuberger et al. 2009 Retrospective cohort study; mortality data from Oklahoma State Department of Health; 1999–2001	5.8	Tuberculosis	SMR: 0.0 (0.0, 10.80)
		Bronchitis, emphysema, asthma	SMR: 1.10 (0.863, 13.84)
		Kidney disease	SMR: 0.984 (0.573, 1.576)

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Schober et al. 2006 Longitudinal study; n=9,757 (NHANES III; age ≥40 years)	Tertiles • T1: <5; mean 2.6 • T2: 5–9; mean 6.3 • T3: >10, mean 11.8	All-cause mortality[c]	**RR T2: 1.24 (1.05, 1.48)*** **RR T3: 1.59 (1.28, 1.98); p-trend<0.001**
Weisskopf et al. 2009 Longitudinal study; n=868 men (Normative Aging Study; age 21–80 years)	Mean (SD): 5.6 (3.4) Tertiles: • T1: <4 • T2: 4–6 • T3: >6	All-cause mortality[c]	Adjusted HR • T1: 1 (reference) • T2: 0.99 (0.71–1.37) • T3: 1.01 (0.71–1.44) p-trend=0.92
PbB >10 µg/dL			
Chowdhury et al. 2014 Survey study; n=58,368 male workers (mean age 38.9 years)	Quartiles • Q1: 0- <5 • Q2: 5- <25 • Q3: 25- <40 • Q4: ≥40	All-cause mortality[c]	**SMR Q4: 0.80 (0.75, 0.84)** SMR overall: 0.69 (0.66, 0.71)
		Chronic obstructive pulmonary disease	SMR Q4: 0.86 (0.64, 1.12) SMR overall: 0.65 (0.54, 0.78)
		Chronic renal disease	SMR Q4: 1.01 (0.58, 1.64) SMR overall: 0.65 (0.44, 0.93)
Cooper 1988; Cooper et al. 1985 Cohort study; n=4,519 battery workers; 2,300 smelters	Mean • Battery (n=1326): 62.7 • Smelters (n=537): 79.7	Nonmalignant respiratory disease	Battery PMR: 0.90 (0.74, 1.10) Smelter PMR: 0.76 (0.53, 1.11)
		Cirrhosis of the liver	Battery PMR:1.29 (0.96, 1.73) Smelter PMR: 0.63 (0.35, 1.15)
		Chronic or unspecified nephritis	**Battery PMR: 2.06 (1.26, 3.18)*; p<0.01** Smelter PMR: 1.86 (0.80, 3.66)
		Chronic nephritis	Battery PMR: 1.48 (0.88, 2.49) Smelter PMR: 1.20 (0.50, 2.86)

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Kim et al. 2015 Cross-sectional study; n=81,067 inorganic Pb workers (54,788 males; 26,279 females; age 20–≤50 years)	Mean (SD) • Males: 8.8 (8.5) • Females 5.8 (5.4) Tertiles: • T1: <10 • T2: 10–20 • T3: >20	All-cause mortality[c]	**Males: RR T3: 1.36 (1.03, 1.79)*; p<0.05** Females: RR T3: 1.30 (0.41, 4.16)
		Non-malignant death	Males: RR T3: 0.95 (0.56, 1.51) Females RR T3: 0.99 (0.13, 7.19)
		Infection	**Males: RR T2: 3.73 (1.06, 13.06)*; p<0.05** Females: Not reported
		Endocrine disease	Males: RR T3: 4.25 (0.90, 20.04)*; p<0.1 Females: Not reported
		Respiratory disease	Males: RR T2: 1.46 (0.28, 7.49) Females: RR T2: 3.49 (0.31, 39.05)
		Digestive disease	**Males: RR T3: 3.23 (1.33, 7.86)*; p<0.05** Females: RR T2: 3.66 (0.33, 40.70)
Lundstrom et al. 1997 Retrospective cohort study; n=3,979 workers	Mean: • In 1950: 62.2 • In 1987: 33.2	All-cause mortality[c]	Total cohort SMR: 0.9 (0.8, 1.0)
		Respiratory disease	Total cohort SMR: 0.4 (0.2, 0.8)
		Digestive organs	Total cohort SMR: 0.6 (0.3, 1.1)
Lustberg and Silbergeld 2002 Longitudinal study; n=4,292; age 30–74 years (NHANES II)	Tertiles: • T1 (n=818): <10 • T2 (n=2,735): 10–19 • T3 (n=637): 20–29	All-cause mortality[c]	RR T2: 1.17 (0.90, 1.52) **RR T3: 1.46 (1.14, 1.86)***
Malcolm and Barnett 1982 Retrospective cohort study; n=754 Pb battery workers	Group1 (non-occupational exposed): not reported Group 2: (light occupational lead exposure): mean 57 Group 3: (high occupational lead exposure): not reported	All-cause mortality[c]	Group 3 SMR: 1.07; p=0.134

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
McDonald and Potter 1996 Prospective cohort study; n=454 pediatric patients diagnosed with Pb poisoning, Massachusetts, 1923–1966, followed through 1991	Mean 113	Diseases of the blood and blood forming organs	**SMR: 9.68 (1.95, 28.28)***
		Nervous-system and sense-organ diseases	SMR: 2.86 (0.57, 8.35)
		Respiratory diseases	SMR: 1.95 (0.78, 4.02)
		Pneumonia	SMR: 2.10 (0.68, 4.90)
		Digestive system diseases	SMR: 1.37 (0.44, 3.21)
		Genitourinary system diseases	SMR: 1.69 (0.02, 9.43)
		Chronic nephritis	SMR: 5.00 (0.06, 27.82)
		All-cause mortality[c]	**SMR: 1.74 (1.40, 2.15)***
McElvenny et al. 2015 Cohort study; n=9,122 workers; mean age 29.2 years	Mean (SD): 44.3 (22.7) Range: 2.3–321.5	All-cause mortality[c]	**Males: SMR 1.10 (1.06, 1.14)*** Females: SMR 1.00 (0.91, 1.09) **Total SMR: 1.09 (1.05, 1.12)***
		Respiratory system diseases	**Males: SMR: 1.17 (1.06,1.30)*** Females: SMR: 1.24 (0.98, 1.57) **Total SMR: 1.18 (1.08, 1.30)***
		Digestive system diseases	**Males: SMR: 1.22 (1.03, 1.45)*** Females: SMR: 0.84 (0.52, 1.35) Total SMR: 1.16 (0.99, 1.36)
		Genitourinary diseases	Males: SMR: 1.02 (0.72,1.44) Females: SMR: 0.67 (0.28, 1.60) Total SMR: 0.95 (0.69, 1.31)
		Non-malignant kidney disease	Males: SMR: 1.30 (0.76, 2.24) Total SMR: 1.29 (0.79. 2.11

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Selevan et al. 1985 Retrospective cohort study; n=1,987 male workers	Mean: 56.3	All tuberculosis	SMR: 1.39 (0.69, 2.49)
		Diseases of the central nervous system	SMR: 0.84 (0.61, 1.12)
		Diseases of the respiratory system	SMR: 1.25 (0.92, 1.66)
		Other respiratory diseases	**SMR: 1.87 (1.28, 2.64)***
		Diseases of the digestive system	SMR: 0.51 (0.26, 0.89)
		Diseases of the genitourinary system	SMR: 0.93 (0.42, 1.77)
		Chronic and unspecified nephritis and other renal sclerosis	SMR: 1.92 (0.88, 3.64)
		All other	SMR: 0.88 (0.67, 1.14)
Steenland et al. 1992 Cohort study (same cohort as Selevan et al. 1985); n=1,990 male smelter workers	Mean: 56.3	All-cause mortality[c]	**SMR: 1.07 (1.00, 1.14)***
		Non-malignant respiratory disease	**SMR: 1.44 (1.16, 1.77)***
		Emphysema	**SMR: 2.20 (1.45, 3.20)***
		Pneumonia and other respiratory disease	**SMR: 1.88 (1.34, 2.56)***
		Acute kidney disease	SMR: 0.91 (0.02, 5.07)
		Chronic kidney disease	SMR: 1.26 (0.54, 2.49)

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Wong and Harris et al. 2000 Cohort study; n=4,519 battery workers; 2,300 smelters (same cohort as Cooper et al. 1985)	Mean: • All workers: 64.0 • Battery workers: 62.7 • Smelters: 79.7	All-cause mortality[c]	**SMR: 1.045 (1.012, 1.08)*; p<0.01**

[a]Studies assessing death due to cardiovascular disease and cancer are discussed in Sections 2.5 and 2.19, respectively.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Includes cancer and/or cardiovascular deaths.

CI = confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PbB = blood lead concentration; PMR = proportionate mortality ratio; RR = rate ratio or relative risk; SD = standard deviation; SE = standard error; SMR = standard mortality ratio

2.4 BODY WEIGHT

Overview. Compared to other health effect endpoints, there is little information on Pb exposure and body weight measures. However, a few epidemiological studies have evaluated effects of Pb exposure on body weight in children, adolescents, and adults. The studies reviewed below focused on effects at PbB ≤10 μg/dL. Negative associations have been observed between PbB and BMI, and decreased risks of being overweight or obese have been reported. However, some studies did not observe associations and one study reported a positive association between PbB and the risk of obesity in women.

Note that studies evaluating the effects of exposure to Pb on birth weight are reviewed in Section 2.18 (Developmental).

The following effects on body weight have been associated with PbB ≤10 μg/dL:

- Decreased BMI and risk of being overweight or obese in children and adolescents; observed in a few studies.
- Decreased BMI and risk of being overweight or obese in adults; not corroborated.
- Increased risk of obesity in women; not corroborated.

Measures of Exposure. Most studies evaluating effects of chronic Pb exposure on body weight evaluate exposure by measurement of PbB. A few other studies examining associations between Pb exposure and body weight used Pb concentration in urine, bone, and/or dentin as biomarkers of exposure; however, these studies did not report PbB (Kim et al. 1995; Padilla et al. 2010; Shao et al. 2017).

Confounding Factors. Numerous confounding factors contribute to body weight (or BMI), including age, sex, race, nutrition, diet, daily activity level, intercurrent illness, genetic pre-disposition for body type, income level, education, and alcohol and tobacco use. Including confounders in a regression model will attenuate apparent associations between Pb exposure and body weight, whereas failure to account for important effect modifiers will result in overestimation of the apparent strength of the association.

Effects at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating effects of PbB ≤10 µg/dL on body weight are briefly summarized in Table 2-2 and an overview of results is provided in Table 2-3; study details are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 1. Studies have been conducted in children and adolescents (Burns et al. 2017; Cassidy-Bushrow et al. 2016; Hauser et al. 2008; Scinicariello et al. 2013) and adults (Scinicariello et al. 2013; Wang et al. 2015). The largest study evaluating associations between PbB and body weight is a study of children, adolescents, and adults participating in NHANES, 1999–2006; this study included adjustments for numerous confounding factors (see the *Supporting Document for Epidemiological Studies for Lead*, Table 1) (Scinicariello et al. 2013). In children and adolescents (n=10,693), results show a negative association between PbB and BMI-Z score and decreased risks of being overweight or obese. In a smaller study in children (n=131), negative associations were observed between PbB and BMI and BMI-Z score (Cassidy-Bushrow et al. 2016). Other studies in small populations of boys showed no associations between weight, BMI and/or BMI-Z score (Burns et al. 2017; Hauser et al. 2008). Results of studies in adults are mixed. The largest study in adults (n=15,899) shows negative associations between PbB and decreased BMI, with a negative trend (p-trend: ≤0.01) over quartiles, and decreased risks of being overweight or obese (Scinicariello et al. 2013). No association was observed between PbB and BMI in a small study on women (n=107) (Ronco et al. 2010) or a larger study in men (n=2235) (Wang et al. 2015). In contrast, the risk of being obese was increased in a large population (n=3323) of women (Wang et al. 2015). Thus, except for the Wang et al. (2015) study, available studies show either no association or a negative association between PbB ≤10 µg/dL and body weight and/or BMI.

Mechanisms of Action. The mechanisms involved in the development of Pb-induced changes in body weight have not been established. However, alterations of the hypothalamic-pituitary-adrenal axis, stress-induced elevations in glucocorticoid levels, oxidative stress, and altered lipid metabolism have been proposed (reviewed by Scinicariello et al. 2013; Shao et al. 2017; Wang et al. 2015).

Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Burns et al. 2017 Prospective cohort of 481 Russian boys enrolled at age 8–9 years and followed until age 18 years	Median 3.0	HT-Z score	**Adjusted β (95% CI), HT-Z score per unit lnPbB: -0.26 (-0.40, -0.13); p<0.001***
		BMI-Z score	Adjusted β (95% CI), BMI-Z score per unit lnPbB: -0.14 (-0.31, 0.04); p=0.12
Cassidy-Bushrow et al. 2016 Birth cohort of 131 children, 2–3 years of age	Mean (SD): 2.45 (2.53)	BMI	**Adjusted RR (95% CI) for BMI ≥85th percentile 0.57 (0.33, 0.98); p=0.041***
		BMI-Z score	**Adjusted β (95% CI) for BMI Z-score: -0.35 (-0.60, -0.10); p=0.012***
Hauser et al. 2008 Cross-sectional study of 489 boys, 8–9 years of age	Mean: 3	Weight	Adjusted β (95% CI), per unit log-PbB: -0.761 (-1.54, 0.02); p=0.067
		BMI	Adjusted β (95% CI), per unit log-PbB: -0.107 (-0.44, 0.23); p=0.53
Ronco 2010 Cross-sectional study of 107 women of childbearing age (median age: 27 years) from Chile; data collection period not reported	Median • All: 1.0 • Low weight: 1.7 • Normal weight: 2.3 • Overweight: 1.0	BMI	No differences in PbB were observed between BMI categories

Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Scinicariello et al. 2013 Cross-sectional study of children and adolescents (n=10,693; age 3–19 years) adults (n=15,899, age ≥20 years) using NHANES data (1999–2006)	Gmean (SE) • Children/adolescents: 1.12 (0.02) • Adults: 1.59 (0.02) • Quartiles (all): ○ Q1: ≤0.70 ○ Q2: 0.71–1.09 ○ Q3: 1.10–1.60 ○ Q4: ≥1.61	BMI-Z score (children and adolescents)	**Adjusted β (SE) (BMI Z-score per PbB quartile):** • **Q3: −0.15 (0.06); p=0.01*** • **Q4: -0.33 (0.07); p ≤ 0.01*** • **p-trend: ≤0.01***
		Overweight (children and adolescents)	**Adjusted OR for Q4: 0.67 (0.52, 0.88)***
		Obesity (children and adolescents)	**Adjusted OR** • **Q3: 0.70 (0.54, 0.90)*** • **Q4: 0.42 (0.30, 0.59)***
		BMI (adults)	**Adjusted β (SE) (BMI per quartile):** • **Q2: −0.90 (0.20); p ≤ 0.01*** • **Q3: −1.41 (0.22); p ≤0.01*** • **Q4: −2.58 (0.25); p ≤0.01*** • **p-trend: ≤0.01***
		Overweight (adults)	**Adjusted OR for Q4: 0.79 (0.65-0.95)***
		Obesity (adults)	**Adjusted OR** • **Q2: 0.76 (0.66–0.87)*** • **Q3: 0.66 (0.56–0.77)*** • **Q4: 0.42 (0.35–0.50)***

Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Wang et al. 2015 Cross-sectional study of 5,558 adults (men: 2,235, ages 39–65 years; women: 3,323, ages 40–65 years) from 16 locations in China	**PbB:** Men • Median: 4.40 • Quartiles: ○ Q1: ≤2.90 ○ Q2: 2.90–4.40 ○ Q3: 4.40–6.22 ○ Q4: ≥6.23 Women: • Median: 3.78 • Quartiles: ○ Q1: ≤2.51 ○ Q2: 2.51–3.77 ○ Q3: 3.78–5.43 ○ Q4: ≥5.44	BMI	β (SE) per PbB quartile • Men ○ Q4: 0.01 (0.20) ○ p-trend: 0.82 • **Women** ○ **Q4: 0.59 (0.17); p<0.05*** ○ **p-trend: <0.001***
		Overweight	Adjusted OR • Men ○ Q4: 0.95 (0.72,1.26) ○ p-trend: 0.74 • Women ○ Q4: 1.16 (0.92, 1.46) ○ p-trend: 0.07
		Obesity	Adjusted OR • Men ○ Q4: 0.88 (0.48, 1.61) ○ p-trend: 0.99 • **Women** ○ **Q4: 1.86 (1.16, 2.98)*** ○ **p-trend: <0.01***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 1 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb.

BMI = body mass index; BMI-Z = BMI z-scores; CI = confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; RR = risk ratio; SD = standard deviation; SE = standard error

Table 2-3. Effects on Body Weight Associated with Mean Blood Lead Concentrations (PbBs) ≤10 µg[a]

Mean PbB (µg/dL)	Population (n)[b]	Weight	BMI	BMI-Z score	Overweight	Obese	Reference
3.0	C (481 boys)	–	–	0	–	–	Burns et al. 2017
2.45	C (131)	–	↓	↓	–	–	Cassidy-Bushrow et al. 2016
3	C (489 boys)	0	0	–	–	–	Hauser et al. 2008
1.0	A (107 women)	–	0	–	–	–	Ronco et al. 2010
1.12	C, Ad (10,693)[c]	–	–	↓	↓	↓	Scinicariello et al. 2013
1.59	A (15,899)[c]	–	↓	–	↓	↓	Scinicariello et al. 2013
4.40	A (2,235, men)	–	0	–	0	0	Wang et al. 2015
3.78	A (3,323, women)	–	0	–	0	↑	Wang et al. 2015

[a]↑ = increased; ↓ = decreased; 0 = no change; – = not assessed.
[b]Unless otherwise specified, study was conducted in males and females.
[c]Participants from the National Health and Nutrition Examination Survey 1999–2006.

A = adults; Ad = adolescents; BMI = body mass index; BMI-Z = BMI z-scores; C = children

2.5 RESPIRATORY

Overview. Few epidemiological studies have evaluated respiratory effects associated with exposure to Pb; those that are available include cross-sectional studies in adults and prospective and cross-sectional studies in children. Associations have been observed between PbB and decreased lung function, increased bronchial hyperreactivity, increased number and severity of symptoms of respiratory disease, and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease). Although most studies found associations between respiratory effects and PbB, other studies did not observe associations.

The following respiratory effects have been associated with PbB:

- ≤10 µg/dL:
  - Decreased lung function; corroborated in a few studies.
  - Increased bronchial hyperreactivity.
  - Increased risk of asthma and obstructive lung disease; evaluated in a few studies with mixed results.

- >10 μg/dL:
    - Decreased lung function.
    - Symptoms of respiratory disease (e.g., shortness of breath).
    - Increased risk/prevalence of asthma; evaluated in a few studies with mixed results.

Measures of Exposure. Studies evaluating the association between respiratory effects and Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors. The etiology for most respiratory diseases is multifactorial; therefore, several co-variables and confounding factors may contribute to clinical findings. Confounding factors that may contribute to the development of respiratory diseases include poor housing conditions, exposure to allergens (e.g., pet dander, seasonal allergies), exposure to tobacco smoke and other respiratory irritants, and asthma compounded by obesity (Ali and Ulirk 2013). In addition, Aligne et al. (2000) reported that children living in urban settings have an increased risk of asthma. Including confounders in a regression model will attenuate the apparent association between Pb exposure and the measured health outcome, whereas failure to account for important effect modifiers (e.g., poor housing conditions, exposure to allergens) will result in overestimation of the apparent strength of the association.

Characterization of Effects. General trends for studies showing a relationship between PbB and respiratory effects are shown in Table 2-4. Compared to other toxicological endpoints (e.g., neurological or cardiovascular effects), few studies have evaluated adverse respiratory effects associated with PbB. Data are from cross-sectional studies in adults (Bagci et al. 2004; Bener et al. 2001; Chung et al. 2015; Min et al. 2008a; Pugh Smith and Nriagu 2011; Rokadia and Agarwal 2013), and prospective (Joseph et al. 2005; Rabinowitz et al. 1990) and cross-sectional (Wells et al. 2014) studies in children. Over the PbB range from ≤10 to >50 μg/dL, studies provide evidence for effects in Pb workers compared to controls or associations between PbB and decreased pulmonary function tests indicative of obstructive pulmonary disease (forced expiratory volume in 1 second [FEV_1], FEV_1/forced vital capacity [FVC] ratio, forced expiratory flow at 25–75% of FVC [FEF_{25-75}]), increased bronchial hyperreactivity (indicative of asthma), symptoms of respiratory disease (cough, shortness of breath), and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease). With the exception of a prospective study in children, which showed no increased risk of asthma at umbilical cord PbB ≥10 μg/dL compared to <10 μg/dL (Rabinowitz et al. 1990), studies showed positive associations between PbB and respiratory effects.

Table 2-4. Overview of Respiratory Effects in Adults and Children Chronically Exposed to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Decreased lung function	Chung et al. 2015
	Increased bronchial responsiveness	Min et al. 2008a
	Lung disease (asthma and obstructive lung disease)	Joseph et al. 2005; Rokadia and Agarwal 2013; Wells et al. 2014
>10–30	Lung disease (asthma)	Pugh Smith and Nriagu 2011
>30–50	Decreased lung function	Bagci et al. 2004
>50	Symptoms of lung disease (phlegm)	Bener et al. 2001
	Lung disease (asthma)	Bener et al. 2001

Effect at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating respiratory effects of PbB ≤10 µg/dL are summarized in Table 2-5, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 2. Studies show associations between PbB ≤10 µg/dL and decreased lung function, increased bronchial hyperreactivity, and increased risk of asthma; findings are consistent with obstructive lung disease. In adults, a cross-sectional study evaluating lung function showed an increased FEV_1/FVC ratio in a population with mean PbB of 2.50 µg/dL; results are consistent with obstructive airway disease (Chung et al. 2015). Increased bronchial reactivity in response to methacholine challenge, consistent with a diagnosis of asthma, was observed in adults with mean PbB of 2.96 µg/dL (Min et al. 2008a). In addition, risk of obstructive lung disease was observed in a large NHANES population of adults with a mean PbB of 1.73 µg/dL (Rokadia and Agarwal 2013). Studies in children examining associations between PbB and risk of asthma do not provide consistent results. A large prospective study showed an increased risk of asthma in black children with PbB <5 and ≥5 µg/dL compared to white children with PbB <5 µg/dL; however, no increased risk was observed for white children with PbB ≥5 µg/dL compared to white children with PbB <5 µg/dL. A large cross-sectional study of children participating in NHANES did not observe an association between PbB (mean 1.07 µg/dL) and asthma, with or without atopy (Wells et al. 2014).

Table 2-5. Summary of Epidemiological Studies Evaluating Respiratory Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Decreased lung function			

Chung et al. 2015
 	
Cross-sectional study; n=870 adults
	• Mean: 2.50
	• Tertiles:
	  ○ T1: <2.03
	  ○ T2: 2.03–2.81
	  ○ T3: >2.81
		FVC%	Correlation coefficient: 0.070

		FEV_1%	Correlation coefficient: 0.00
		FEV_1/FVC ratio	**Correlation coefficient: -0.115; p<0.01***
			OR T3: 0.006 (0, 0.286)*
			p-trend: 0.03*
Increased bronchial responsiveness			
Min et al. 2008a Cross-sectional study; n=523 adults	Mean (SD): 2.96 (1.59)	BR	**A 1 µg/dL increase in PbB was associated with a higher BR; β (SE): 0.018 (0.007).***
Asthma			
Joseph et al. 2005 Prospective study; n=4,634 children (ages 3 months to 3 years)	Mean • White: 3.2 • Black: 5.5	Asthma	All compared to PbB <5 µg/dL in white children
			HR white (PbB ≥5): 2.3 (0.8, 6.7); p=0.12
			HR black (PbB <5): 1.8 (1.3, 2.4); p<0.01*
			HR black (PbB ≥5): 1.5 (1.2, 1.8); p<0.01*
			HR black (PbB ≥10): 3.0 (1.2, 7.1); p=0.01*
Rokadia and Agarwal 2013[c] Pooled cross-sectional study; n=9,575 adults (8,411 without OLD; 1,164 with OLD)	Mean • Non-OLD: 1.18 • OLD: 1.73	OLD	**OR for all OLD: 1.94 (1.10, 3.42)***
			OR for mild OLD: 1.21 (0.55, 2.65)
			OR for moderate-severe OLD: 3.49 (1.70, 7.15)*

Table 2-5. Summary of Epidemiological Studies Evaluating Respiratory Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Wells et al. 2014[c] Cross-sectional study; NHANES 2005–2006; n=1,430 children (ages 4–12 years)	Geometric mean: 1.07	Asthma	OR for asthma with atopy: 0.97 (0.61, 1.55) OR for asthma with no atopy: 1.07 (0.86, 1.33)

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 2 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Study population was from NHANES.

BR = bronchial responsiveness; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second (L/s); FEV_1% = percent of predicted FEV_1; FVC = forced vital capacity (L); FVC% = percent of predicted FVC; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OLD = obstructive lung disease; OR = odds ratio; SD = standard deviation; SE = standard error

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of toxicity to the respiratory system. EPA (2014c) specifically noted that oxidative stress through reactive oxygen species (ROS), resulting in tissue damage and inflammation and immune effects, is a plausible mechanism for the underlying cause of respiratory damage. Increased ROS, along with depletion of antioxidants, results in inflammation and production and release of metabolites and cytokines. Immune-mediated inflammation is observed with asthma and bronchial hyperreactivity.

2.6 CARDIOVASCULAR

Overview. A large number of epidemiological studies showing adverse effects on the cardiovascular system associated with Pb exposure have been published. Most studies evaluated effects in adults, although a few studies in children have been conducted. The effect of Pb exposure on blood pressure is the most studied cardiovascular outcome, with results providing consistent evidence of positive associations between lead exposure and blood pressure. Other cardiovascular endpoints (atherosclerosis, cardiac conduction, cardiovascular disease, and mortality due to cardiovascular disease) also show positive and negative associations with PbB, although the majority of studies had positive associations. In some cases, although no associations between PbB and cardiovascular outcomes were observed, associations were observed for bone Pb, a biomarker of cumulative lead exposure that, among individuals with high historical lead exposures, typically remains elevated for many years after the PbB declines to ≤10 μg/dL; these cases are noted in the discussions below.

The following cardiovascular effects have been associated with PbB:

- ≤10 μg/dL:
    - Greater systolic and diastolic blood pressure:
        - In adults; corroborated in multiple studies.
        - In children; evaluated in a few studies.
        - During pregnancy; evaluated in a few studies.
    - Greater risk of hypertension:
        - In adults; evaluated in a few studies.
        - During pregnancy; evaluated in a few studies
    - Greater risk of atherosclerosis; evaluated in a few studies.
    - Altered cardiac conduction; evaluated in a few studies.

  - Greater risk of mortality due to cardiovascular diseases; evaluated in a few studies with mixed results.
- >10 μg/dL:
  - Increased systolic and diastolic blood pressure:
    - In adults; corroborated in multiple studies and meta-analyses.
    - In children; evaluated in a few studies.
  - Increased risk of hypertension; corroborated in multiple studies.
  - Atherosclerosis; evaluated in a few studies.
  - Increased risk or prevalence of heart disease; evaluated in a few studies.
  - Increased mortality due to cardiovascular diseases; corroborated in multiple studies.

Measures of Exposure. PbB and bone Pb concentrations have been used as biomarkers to evaluate cardiovascular effects of Pb exposure. However, PbB may not provide the ideal biomarker for long-term exposure to target tissues that contribute a hypertensive effect of Pb. Because the development of cardiovascular effects has a long latency period, associations between PbB and cardiovascular disease at concurrent PbB ≤10 μg/dL may be related to higher past Pb exposures. Bone Pb, a metric of cumulative or long-term exposure to Pb, appears to be a better predictor of Pb-induced elevations in blood pressure and alterations in cardiac conduction than PbB.

Confounding Factors. Numerous co-variables and confounders affect studies of associations between PbB and blood pressure, including age, body mass, race, smoking, alcohol consumption, ongoing or family history of cardiovascular/renal disease, LDL cholesterol levels, and various dietary factors (e.g., dietary calcium). In addition, renal disease, as well as Pb-induced renal damage, can lead to cardiovascular effects, including increased blood pressure (EPA 2014c; NTP 2012); thus, interpretation of studies examining cardiovascular outcomes is complicated by the link between cardiovascular and renal function. Including confounders in a regression model will attenuate the apparent association between Pb exposure and the measured health outcome (e.g., Møller and Kristensen 1992). For example, adjusting for alcohol consumption will decrease the apparent association between PbB and blood pressure, if alcohol consumption contributes to Pb intake and, thereby, PbB (Bost et al. 1999; Hense et al. 1993; Hertz-Picciotto and Croft 1993; Wolf et al. 1995). Conversely, failure to account for important effect modifiers (e.g., inherited disease) will result in overestimation of the apparent strength of the association. Varying approaches and breadth of inclusion of these may account for the disparity of results that have been reported. Measurement error may also be an important factor. Blood pressure estimates based on

multiple measurements or, preferably, 24-hour ambulatory measurements, are more reproducible than single measurements (Staessen et al. 2000).

Characterization of Effects. General trends between studies showing a relationship between PbB and cardiovascular effects are shown in Table 2-6. Over the PbB range of ≤10–>50 μg/dL, results of epidemiological studies provide evidence for increased blood pressure and hypertension, atherosclerosis (increased intimal medial thickening and peripheral artery disease), heart disease (myocardial infarction, ischemic heart disease, left ventricular hypertrophy, cardiac arrhythmias, and angina), and increased risk of mortality due to cardiovascular diseases. The effect of Pb exposure on blood pressure is the most studied cardiovascular outcome. A review by Navas-Acien et al. (2007) concluded that that available literature provides evidence that "is sufficient to infer a causal relationship of lead exposure and hypertension" and evidence that "is suggestive but not sufficient to infer a causal relationship of lead exposure with clinical cardiovascular outcomes" (cardiovascular, coronary heart disease, and stroke mortality; and peripheral arterial disease). Well-controlled studies in laboratory animals provide additional support regarding effects of Pb on blood pressure; see EPA (2014c) for additional information.

Numerous studies provide a weight of evidence for associations between PbB and increased blood pressure over a wide PbB range in adults (Table 2-6). Results of meta-analyses estimate small but consistent increases in blood pressure per doubling of PbB. The largest meta-analysis of 31 studies published between 1980 and 2001 included a total of 58,518 subjects (Nawrot et al. 2002); blood pressure data from studies included in the analysis are shown in Table 2-7 and Figures Figure 2-2 and Figure 2-3. Nawrot et al. (2002), in an update of an earlier meta-analysis by Staessen et al. (1994), estimated the increase in systolic pressure per doubling of PbB to be 1 mmHg (95% CI 0.5, 1.4) and the increase in diastolic pressure to be 0.6 mmHg (95% CI 0.4, 0.8). The range of mean (or median) PbBs for studies included in the analysis was 2.28–63.82 μg/dL. Although a PbB mean was not estimated for the entire study population, only nine studies had a mean PbB <10 μg/dL; therefore, it is likely that the overall PbB mean for the entire study population was >10 μg/dL. Similar outcomes were observed in two other meta-analyses (Schwartz 1995; Staessen et al. 1994). A meta-analysis reported by Staessen et al. (1994) included 23 studies (published between 1984 and 1993; 33,141 subjects) and found a 1 mmHg (95% CI 0.4, 1.6) increase in systolic blood pressure and 0.6 mmHg (95% CI 0.2, 1.0) increase in diastolic pressure per doubling of PbB. Schwartz (1995) conducted a meta-analysis that encompassed a similar time frame (15 studies published between 1985 and 1993) and found a 1.25 mmHg (95% CI 0.87, 1.63) increase in systolic blood pressure per doubling of PbB (diastolic not reported). The latter analysis included only those studies that reported a standard error (SE) on effect measurement (e.g., increase in

blood pressure per doubling of PbB). Of the 15 studies included in the Schwartz (1995) analysis, 8 were also included in the Staessen et al. (1994) analysis. The estimated increase in blood pressure per doubling of PbB in these meta-analyses is small; however, on a population basis, the consequences of increased blood pressure includes increased risks of serious and potentially fatal effects, including atherosclerosis, stroke, and myocardial infarction. Increased blood pressure during pregnancy has been associated with PbB and bone Pb (Rothenberg et al. 2002b; Wells et al. 2011; Yazbeck et al. 2009); these studies are discussed in more detail below (*Effect at Blood Pb Levels ≤10 µg/dL*).

Table 2-6. Overview of Cardiovascular Effects in Adults and Children Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased blood pressure and hypertension	Al-Saleh et al. 2005; Bost et al. 1999; Bushnik et al. 2014; Cheng et al. 2001; Chu et al. 1999; Den Hond et al. 2002; Elmarsafawy et al. 2006; Faramawi et al. 2015; Gerr et al. 2002; Glenn et al. 2003; Gump et al. 2005, 2011; Hense et al. 1993; Hu et al. 1996a; Korrick et al. 1999; Martin et al. 2006; Muntner et al. 2005; Nash et al. 2003; Park et al. 2009b; Perlstein et al. 2007; Proctor et al. 1996; Rothenberg et al. 2002b; Schwartz 1995; Scinicariello et al. 2010, 2011; Vupputuri et al. 2003; Wells et al. 2011; Yazbeck et al. 2009; Zhang et al. 2011; Zota et al. 2013
	Atherosclerosis[a]	Ari et al. 2011; Muntner et al. 2005; Navas-Acien et al. 2004;
	Heart disease[b]	Cheng et al. 1998; Eum et al. 2011; Jain et al. 2007; Park et al. 2009a
	Mortality due to cardiovascular disease	Aoki et al. 2016; Khalil et al. 2009; Menke et al. 2006; Schober et al. 2006; Weisskopf et al. 2009
>10–30	Increased blood pressure and hypertension	Coate and Fowles 1989; Factor-Litvak et al. 1999; Grandjean et al. 1989; Harlan et al. 1985; Møller and Kristensen 1992; Pirkle et al. 1985; Rabinowitz et al. 1987
	Atherosclerosis[a]	Pocock et al. 1988; Poreba et al. 2011, 2012
	Heart disease[b]	Poreba et al. 2013
	Mortality due to cardiovascular disease	Lustberg and Silbergeld 2002; Schober et al. 2006

Table 2-6. Overview of Cardiovascular Effects in Adults and Children Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>30–50	Increased blood pressure and hypertension	Aiba et al. 1999; Al-Saleh et al. 2005; Factor-Litvak et al. 1996, 1999; Ghiasvand et al. 2013; Glenn et al. 2006; Rapisarda et al. 2016; Weaver et al. 2008; Weiss et al. 1986, 1988
	Heart disease[b]	Bockelmann et al. 2002; Jain et al. 2007
	Mortality due to cardiovascular disease	Gerhardsson et al. 1995a
>50	Increased blood pressure and hypertension	Kirby and Gyntelberg 1985; Were et al. 2014
	Atherosclerosis[a]	Kirby and Gyntelberg 1985
	Mortality due to cardiovascular disease	Cooper 1988; Cooper et al. 1985; Fanning 1988; Gerhardsson et al. 1995a; McDonald and Potter 1996

[a]Atherosclerosis includes increased intimal medial thickening and peripheral artery disease.
[b]Heart disease includes myocardial infarction, ischemic heart disease, left ventricular hypertrophy, cardiac arrhythmias, and angina.

Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number[a]	Population[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
1[h]	Pocock et al. 1984[i,j]; Shaper et al. 1981	7,379	GP	100	Y	49 (40–59)	145	82	15.13 (2.07–66.3)[Ae]
2	Kromhout 1988[i,j]; Kromhout et al. 1985[i]	152	GP	100	Y	67 (57–76)	154	92	18.23 (10.77–27.97)[Ac]
3	Moreau et al. 1982[j], 1988; Orssaud et al. 1985[i,j]	431	WC	100	Y	41 (24–55)	131	75	18.23 (8.91–49.94)[Ae]
4	Weiss et al. 1986[i], 1988[i]	89	WC	100	Y	47 (30–64)	122	83	24.45 (18.65–29.01)[Mx]
5	de Kort and Zwennis 1988[i,j]; de Kort et al. 1987[i]	105	BC	100	N	40 (25–80)	136	83	29.22 (4.35–83.29)[Ae]
6	Lockett and Arbuckle 1987[i]	116	BC	100	Y	32 (?–?)	119	80	37.5 (14.92–95.52)[Ae]
7	Parkinson et al. 1987[i]	428	BC	100	Y	36 (18–60)	127	80	27.97 (6.01–49.52)[Ac]

Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number[a]	Population[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
8	Rabinowitz et al. 1987[i]	3,851	GP	0	Y	28 (18–38)	121	76	7.04 (3.73–10.15)[Ac]
9	Elwood et al. 1988a[i,j], 1988b[k]	1,136	GP	100	Y	56 (49–65)	146	87	12.64 (6.01–26.11)[Gc]
10	Elwood et al. 1988a, 1988b[i,j,l]	1,721	GP	50	Y	41 (18–64)	127	78	10.15 (4.56–23.21)[Gc]
11	Gartside et al. 1988[i]; Harlan 1988; Harlan et al. 1985; Pirkle et al. 1985; Ravnskov 1992[m]	6,289	GP	53	Y	30 (10–74)	127	80	13.47 (2.07–95.93)[Ge]
12	Neri et al. 1988[i,j,n]	288	BC	100	?	? (?–?)	?	?	45.17 (6.01–65.06)[Ae]
13	Neri et al. 1988[i,o]	2,193	GP	?	Y	45 (25–65)	?	?	23.41 (0–47.03)[Me]
14	Grandjean et al. 1989, 1991[i,p]	1,050	GP	48	Y	40 (40–40)	?	?	11.6 (3.94–60.09)[Ae]
15	Reimer and Tittelbach 1989[i]	58	BC	100	?	32 (?–?)	134	81	39.99 (12.85–70.24)[Ac]
16	Apostoli et al. 1990[i]	525	GP	48	Y	45 (21–60)	132	84	13.05 (2.07–28.18)[Ae]
17	Morris et al. 1990[i,j]	251	GP	58	Y	? (23–79)	?	?	7.46 (4.97–38.95)[Ae]
18	Sharp et al. 1988[i,j], 1989[i], 1990[i]	249	WC	100	N	43 (31–65)	128	83	6.63 (2.07–14.92)[Pe]
19	Staessen et al. 1984[i,q]	531	WC	75	Y	48 (37–58)	126	78	11.4 (4.14–35.22)[Ge]
20	Møller and Kristensen 1992[i,j,r]	439	GP	100	Y	40 (40–40)	?	?	13.68 (4.97–60.09)[Ae]
21	Hense et al. 1993[i,j]	3,364	GP	51	Y	48 (28–67)	129	80	7.87 (1.24–37.09)[Ae]
22	Maheswaran et al. 1993[i]	809	BC	100	Y	43 (20–65)	129	84	31.7 (0–98.01)[Ae]
23	Menditto et al. 1994	1,319	GP	100	Y	63 (55–75)	140	84	11.19 (6.22–24.66)
24	Hu et al. 1996a; Proctor et al. 1996[s]	798	GP	100	Y	66 (43–93)	134	80	5.59 (0.41–35.02)[Pe]
25	Staessen et al. 1996a[i], 1996b[i,t]	728	GP	49.3	Y	46 (20–82)	130	77	9.12 (1.66–72.52)[Ge]
26	Sokas et al. 1997[u]	186	BC	99	Y	43 (18–79)	130	85	7.46 (2.07–30.04)[Pe]
27	Bost et al. 1999	5,326	GP	48	Y	48 (16–?)	135	75	63.82 (?–?)[G]

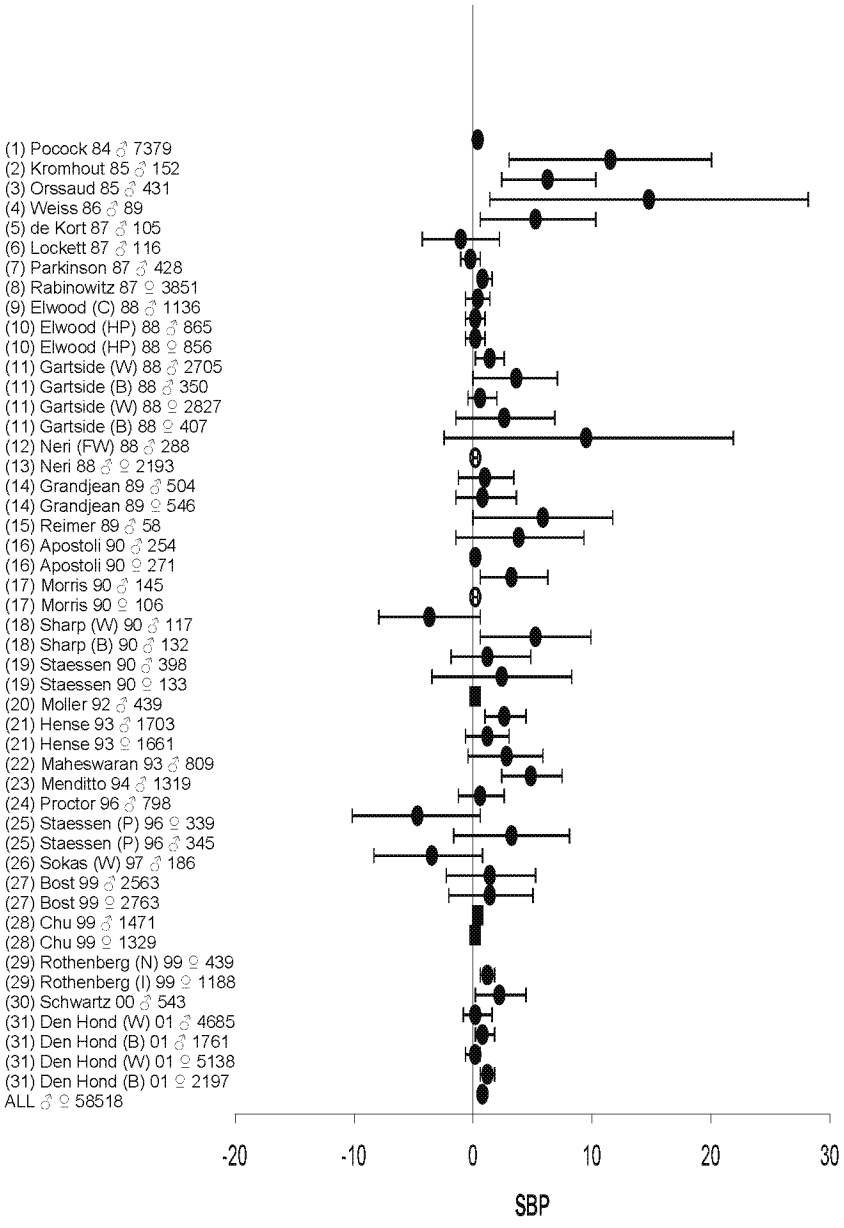
Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number[a]	Population[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
28	Chu et al. 1999	2,800	GP	53	Y	44 (15–85)	123	78	6.42 (0.41–69)[Ae]
29	Rothenberg et al. 1999a, 1999b	1,627	GP	0	Y	27 (?–?)	110	59	2.28 (?–?)[G]
30	Schwartz et al. 2000c	543	BC	100	Y	58 (41–73)	128	77	4.56 (1.04–20.1)[Ae]
31	Den Hond et al. 2001[v]	13,781	GP	53.2	Y	48 (20–90)	125	73	3.11 (0.62–55.94)[Ge]

[a]Number of persons in whom relevant data were available.
[b]Study population: BC = blue collar workers; GP = sample from general population; WC = white collar employees.
[c]Men: Percentage of men.
[d]HT: Indicates whether the sample included (Y = yes) or did not include (N = no) hypertensive patients.
[e]Age: Mean age or midpoint of age span (range or approximate range given between parentheses).
[f]SBP, DBP: Mean systolic and diastolic blood pressures.
[g]Lead: Measure of central tendency: A = arithmetic mean; G = geometric mean; M = midpoint of range; P = P_{50} (median). The spread of blood lead is given between parentheses: c = P_5–P_{05} interval; P_{10}–P_{90} interval, or interval equal to 4 times the standard deviation; e = extremes; x = approximate limits of distribution.
[h]Number refers to reference in Figures Figure 2-2 and Figure 2-3.
[i]Included in the Staessen et al. (1994) meta-analysis.
[j]Included in the Schwartz (1995) meta-analysis.
[k]Caerphilly Study.
[l]Welsh Heart Program.
[m]NHANES (National Health and Nutrition Examination Survey).
[n]Foundry workers.
[o]Canadian Health Survey.
[p]Glostrup Population Study, cross-sectional analysis (1976).
[q]London Civil Servants.
[r]Glostrup Population Study, longitudinal analysis (1976–1987).
[s]Normative Aging Study.
[t]PheeCad (Public Health and Environmental Exposure to Cadmium) Study.
[u]Because of missing information, only the effect in whites is included.
[v]NHANES III Survey.

Source: Nawrot et al. 2002

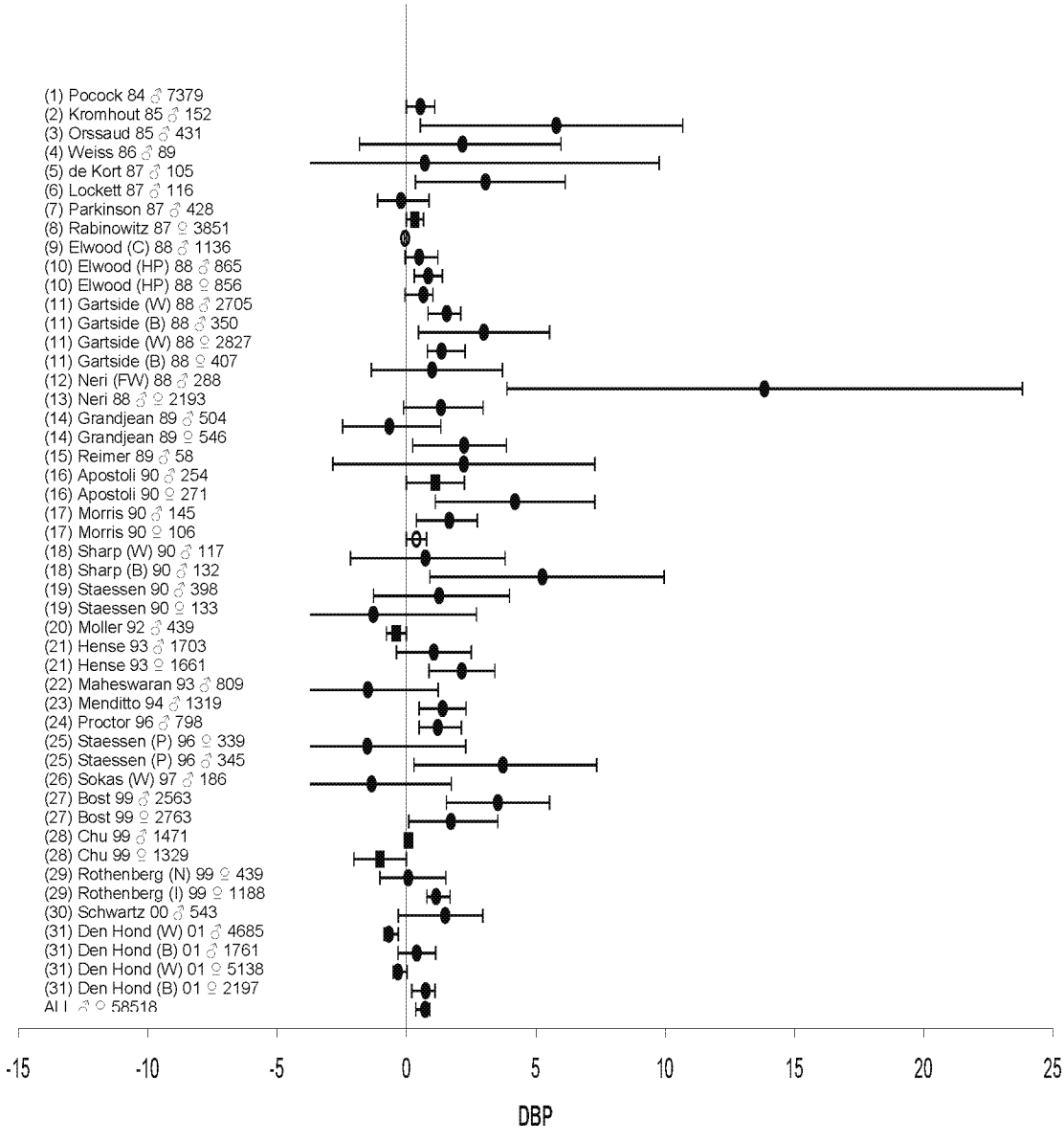
Figure 2-2. Change in the Systolic Pressure Associated with a Doubling of the Blood Lead Concentration (PbB)*



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 2-7 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; NI = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

Figure 2-3. Change in the Diastolic Pressure Associated with a Doubling of the Blood Lead Concentration (PbB)*



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 2-7 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; N = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

Within individual studies, dose-effect relationships are evident at PbB ≤10 μg/dL. A positive dose-effect was observed for PbB and diastolic blood pressure (Zota et al. 2013). An observed positive dose-effect was observed for tibia Pb concentration and hypertension (Hu et al. 1996a). No dose-effect was observed for PbB and pulse pressure (PP), although a positive dose-effect was observed for tibia Pb and PP (Perlstein et al. 2007). In a cross-sectional study of women, diastolic hypertension was observed to have a positive dose-effect when pre- and postmenopausal women were analyzed together and when postmenopausal women were analyzed alone. In contrast, a dose-effect relationship was not observed for PbB and hypertension in a cross-sectional study of men and women (Muntner et al. 2005). A positive dose-effect relationship was observed for PbB and peripheral artery disease (PAD) (Muntner et al. 2005). In men, tibia blood levels had a positive dose-effect relationship with QT interval, but a negative dose-effect relationship with atrioventricular conduction defect (Eum et al. 2011). Studies have also found positive dose-effect relationships between mortality due to cardiovascular disease, myocardial infraction, and stroke and PbB (Menke et al. 2006; Schober et al. 2006).

Several studies have evaluated associations between PbB and cardiovascular function in children (Factor-Litvak et al. 1999, 1996; Gump et al. 2005, 2011; Kapuku et al. 2006; Khalil et al. 2009, 2010; Lustberg and Silbergeld 2002; Menke et al. 2006; Schober et al. 2006; Zhang et al. 2011). Results show alterations in cardiovascular function, including increases in blood pressure and altered cardiovascular function under stress (decreased stroke volume and cardiac output) over a PbB range from <10 to approximately 40 μg/dL.

Effect at Blood Pb Levels ≤10 μg/dL. Studies investigating relationships between PbB ≤10 μg/dL and cardiovascular effects have evaluated effects on blood pressure (including hypertension), atherosclerosis, heart disease (alterations in cardiac conduction and ischemic heart disease), and death due to cardiovascular disease.

Increased blood pressure and hypertension. Numerous studies of large populations show associations between PbB ≤10 μg/dL and increased systolic and/or diastolic blood pressure and increased risk of hypertension (see Table 2-8). The lowest PbB range positively associated with systolic and diastolic blood pressure is 1.41–1.75 μg/dL (Scinicariello et al. 2011). A few studies did not show associations between PbB and blood pressure parameters; however, positive associations between bone Pb concentrations and blood pressure at concomitant PbB ≤10 μg/dL were observed (Gerr et al. 2002; Hu et al. 1996a; Korrick et al. 1999; Zhang et al. 2011). Studies are briefly summarized in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3.

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Women and men combined (not stratified by sex)[c]			
Faramawi et al. 2015[d] Cross-sectional study; n=13,757	Mean: 3.44	SBP	**β (SE), mmHg for change in blood pressure SD per µg/dL: 0.07 (0.02); p<0.01***
		DBP	β (SE), for change in blood pressure SD per µg/dL: 0.04 (0.03); p=0.08
Martin et al. 2006 Cross-sectional study; n=964 (ages 50–70 years)	Mean: 3.5	SBP	**β, mmHg per 1 µg/dL: 0.99 (0.47,1.51); p<0.01***
		DBP	**β, mmHg per 1 µg/dL: 0.51 (0.24, 0.79); p<0.01***
Zota et al. 2013[d] Cross-sectional study; n=8,194 (ages 40–65 years)	Mean: 1.69 Quintiles: • Q1: ≤1.05 • Q2: 1.06–1.44 • Q3: 1.45–1.90 • Q4: 1.91–2.69 • Q5: >2.70	Elevated SBP (≥140 mmHg)	OR (Q5): 1.23 (0.92, 1.65); p-trend: 0.06
		Elevated DBP (≥90 mmHg)	**OR (Q3): 1.56 (1.11, 2.19)*** **OR (Q4): 1.80 (1.24, 2.60)*** **OR (Q5): 1.77 (1.25, 2.50)*** **p-trend 0.0002**
Women and men (stratified by sex)[c]			
Bost et al. 1999 Cross-sectional study; n=2,563 males and 2,763 females	Mean • M: 3.7 • F: 2.6	SBP	M: no association with PbB (regression coefficient not reported)
			F: no association with PbB (regression coefficient not reported)
		DBP	**M: β, per doubling of PbB: 0.78 (0.01, 1.55)***
			F: regression coefficients not reported

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Bushnik et al. 2014 Population-based survey; n=2,214 males and 2,336 females	Mean • All: 1.64 • Non-hypertensive: 1.59 • Hypertensive: 1.74	SBP	All β, mmHg per 1 µg/dL: 1.85 (-0.20, 3.90); p=0.075
			M β, mmHg per 1 µg/dL: 2.17 (-0.08, 4.42); p=0.058
			F β, mmHg per 1 µg/dL: 0.76 (-2.72, 4.24); p=0.656
		DBP	**All β, mmHg per 1 µg/dL: 1.91 (0.75, 3.08); p=0.002***
			M β, mmHg per 1 µg/dL: 2.36 (0.94, 3.79); p=0.002*
			F β, mmHg per 1 µg/dL: 1.43 (-0.51, 3.38); p=0.142
		Hypertension	**All β, mmHg per 1 µg/dL: -3.87 (-7.46, -0.29); p=0.035***
			M β, mmHg per 1 µg/dL: -6.37 (-15.02, 2.29); p=0.142
			F β, mmHg per 1 µg/dL: -4.18 (-8.78, 0.42); p=0.073
Chu et al. 1999 Population-based survey study; n=1,471 males and 1,329 females	Mean • M: 7.3 • F: 5.7	SBP	**M β (SE), mmHg per 1 $\log_{10}$ µg/dL: 0.185 (0.076); p=0.015***
			F β (SE), mmHg per 1 $\log_{10}$ µg/dL: -0.057 (0.109); p=0.603
		DBP	M β (SE), mmHg per 1 $\log_{10}$ µg/dL: 0.075 (0.053); p=0.159
			F β (SE), mmHg per 1 $\log_{10}$ µg/dL: -0.083 (0.072); p=0.250

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Hense et al. 1993 Population-based survey study; n=1,703 males and 1,661 females	Mean • M: 8.3 • F: 6.0	SBP	**M β, mmHg per 1 µg/dL: 0.29 (0.08, 0.49)***
			F β, mmHg per 1 µg/dL: 0.17 (-0.14, 0.48)
		DBP	M β, mmHg per 1 µg/dL: 0.08 (-0.06, 0.23)
			F β, mmHg per 1 µg/dL: 0.29 (0.09, 0.49)*
Men only[c]			
Cheng et al. 2001[e] Longitudinal study; n=833 men Analysis for hypertension limited to 474 participants who had no history of definite hypertension; analysis for SBP limited to 519 participants who were free from definite hypertension at baseline	PbB mean (all): 6.09 Tibia Pb (µg/g) • Borderline: 23.46 • Definite: 22.69 Patella Pb (µg/g) • Borderline: 33.73 • Definite: 32.72	Hypertension (borderline and definite)	RR, per 1 SD increase in PbB: 1.00 (0.76, 1.33)
			RR, per 1 SD increase in tibia Pb: 1.22 (0.95, 1.57)
			RR, per 1 SD increased in patella Pb: 1.29 (1.04, 1.61); p<0.05*
		SBP	RR, per 1 SD increase in PbB: -0.13 (-1.35, 1.09)
			RR, per 1 SD increase in tibia Pb: 1.37 (0.02, 2.73); p<0.05*
			RR, per 1 SD increased in patella Pb: 0.57 (-0.71, 1.84)
Elmarsafawy et al. 2006[e] Cross-sectional study; n=471	Mean • Low Ca^{2+} intake: 6.6 • High Ca^{2+} intake: 6.6	Hypertension	**Low Ca^{2+}: OR: 1.07 (1.00, 1.15)***
			High Ca^{2+}: OR: 1.03 (0.97, 1.11)
Glenn et al. 2003 Occupational longitudinal study; n=496	Mean: 4.6	SBP	**β (SE; 95% CI), per 1 SD increased in PbB: 0.64 (0.25; 0.14, 1.14)***
		DBP	β (SE; 95% CI); per 1 SD increased in PbB: 0.09 (0.17; -0.24, 0.43)

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Hu et al. 1996a[e] Case-control study of men (n=146) with hypertension and controls (n=444)	Mean • Cases: 6.9 • Controls: 6.1	Hypertension	**Risk of hypertension based on tibia Pb: logistic β (SE): 0.19 (0.0078); p=0.01*** PbB was not associated with hypertension
			OR (95% CL) for 1 µg/g change in tibia Pb: 1.019 (1.004, 1.035)*
			OR (95% CL) for quintile range (8–37 µg/g): 1.5 (1.1, 1.8)*
Perlstein et al. 2007[e] Cross-sectional study; n=593	Mean: 6.12	PP	PbB: no trend over quintiles (p=0.82)
			Bone Pb: p-trend=0.02*
Proctor et al. 1996[e] Cross-sectional study; ≤74 years (n=681); >74 years (n=117)	Mean (SD) • All: 6.5 • ≤74 years: 6.5 • >74 years: 6.3	SBP	All β, mmHg per 1 ln µg/dL PbB: 0.85 (-1.1, 2.7); p>0.05
			≤74 β, mmHg per 1 ln µg/dL PbB: 1.2 (-0.86, 3.2); p>0.05
		DBP	**All β, mmHg per 1 ln µg/dL PbB: 1.2 (0.11, 2.2); p≤0.05***
			≤74 β, mmHg per 1 ln µg/dL PbB: 1.6 (0.42, 2.7); p≤0.01*
Women only[c]			
Al-Saleh et al. 2005 Case-control study of women with hypertension (n=100) and control subjects (n=85)	Mean • Hypertension: 4.75 • Controls: 4.56	Hypertension	OR for PbB ≥3.85 compared to PbB <3.85: 5.27 (0.93, 29.86); p=0.06

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Korrick et al. 1999 Case-control study of women with hypertension (n=89) and control subjects (n=195)	Mean (all): 3	Hypertension	PbB: no increased risk (ORs not reported)
			Patella Pb OR per 1 µg/g increase in PbB: 1.03 (1.00, 1.05); p=0.02*
Nash et al. 2003 Cross-sectional study; n=2,165 all; 1,084 premenopausal, and 663 postmenopausal	Mean (all): 2.9 Quartiles; mean (range) • Q1: 1.0 (0.5–1.6) • Q2: 2.1 (1.7–2.5) • Q3: 3.2 (2.6–3.9) • Q4: 6.4 (4.0–31.1)	SBP	**All β (SE), mmHg per 1 ln µg/dL PbB: 0.32 (0.16); p=0.03***
			Premenopausal β (SE), mmHg per 1 ln µg/dL PbB: 0.14 (0.26); p=0.59
			Postmenopausal β (SE), mmHg per 1 ln µg/dL PbB: 0.42 (0.21); p=0.29
		DBP	**All β (SE): 0.25 (0.09), mmHg per 1 ln µg/dL PbB; p=0.009***
			Premenopausal β (SE), mmHg per 1 ln µg/dL PbB: 0.38 (0.25); p=0.12
			Postmenopausal β (SE) mmHg per 1 ln µg/dL PbB: 0.14 (0.13); p=0.04*
		Hypertension	**Percent of total population with hypertension: p-trend<0.001** (Q1: 19.4; Q2: 20.6; Q3: 25.5 Q4: 28.3)

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Women and men stratified by race[c]			
Den Hond et al. 2002[d] Cross-sectional study n=4,685 MW; 5,138 FW; 1,761 MB; and 2,197 FB	Mean • MW: 3.6 • FW: 2.1 • MB: 4.2 • FB: 2.3	SBP	MW β, per doubling of PbB: 0.3 (-0.2, 0.7); p=0.29
			FW β, per doubling of PbB: 0.1 (-0.4, 0.5); p=0.80
			MB β, per doubling of PbB: 0.9 (0.04,1.8); p=0.04*
			FB β, per doubling of PbB: 1.2 (0.4,2.0); p=0.004*
		DBP	**MW β, per doubling of PbB: -0.6 (-0.9, -0.3); p=0.0003***
			FW β, per doubling of PbB: -0.2 (-0.5, 0.1); p=0.13
			MB β, per doubling of PbB: 0.3 (-0.3, 1.0); p=0.28
			FB β, per doubling of PbB: 0.5 (0.01, 1.1); p=0.047*
Muntner et al. 2005[d] Cross-sectional study of 9,961 (men and women), stratified by race (W, B, MA)	Mean: 1.64 Quartiles: • Q1: <1.06 • Q2: 1.06–1.63 • Q3: 1.63–2.47 • Q4: ≥2.47	Hypertension	W (Q4) OR: 1.10 (0.87, 1.41); p-trend=0.61
			B (Q4) OR: 1.44 (0.89, 2.32); p-trend=0.06
			MA (Q4) OR: 1.54 (0.99, 2.39); p-trend=0.04*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Park et al. 2009b[d] Cross-sectional study; n=12,500 all, 2,130 MW (<50 years old); 2,152 MW (≥50 years old); 1,048 MB (<50 years old); 540 MB (≥50 years old); 2,429 FW (<50 years old); 2,180 FW (≥50 years old); 1,409 FB (<50 years old); and 612 FB (≥50 years old)	Mean • MW (<50 years old) 4.02 • MW (≥50 years old) 4.92 • MB (<50 years old) 4.55 • MB (≥50 years old) 7.57 • FW (<50 years old) 2.09 • FW (≥50 years old) 3.53 • FB (<50 years old) 2.52 • FB (≥50 years old) 4.49	Hypertension	MW OR: 1.06 (0.92, 1.22)
			FW OR: 1.16 (1.04, 1.29)*
			MB OR: 1.17 (0.98, 1.38)
			FB OR: 1.19 (1.04, 1.38)*
			M (<50 years old) OR: 0.98 (0.80, 1.22)
			M (>50 years old) OR: 1.20 (1.02, 1.41)*
			F (<50 years old) OR: 1.23 (1.04, 1.46)*
			F (>50 years old) OR: 1.09 (0.94, 1.26)
Scinicariello et al. 2010[d] Cross-sectional study; n=6,016 (stratified by race)	Mean • W 2.87 • B 3.59 • MA 3.33	SBP	**W β (SE), mmHg per ln µg/dL PbB: 1.05 (0.37); p=0.01***
			B β (SE), mmHg per ln µg/dL PbB: 2.55 (0.49); p=0.001*
			MA β (SE), **mmHg per ln µg/dL PbB**: 0.84 0.46); p=0.08
		DBP	W β (SE), **mmHg per ln µg/dL PbB**: -0.14 0.49); p=0.77
			B β (SE), mmHg per ln µg/dL PbB: 1.99 (0.44); p=0.0002*
			MA β (SE), **mmHg per ln µg/dL PbB**: 0.74 0.74); p=0.06

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Scinicariello et al. 2011[d] Cross-sectional study; n=16,222 all; 4,538 MW; 4,319 FW; 1,767 MB; 1,854 FB; 1,925 MMA; and 1,819 FMA	Mean • All 1.41 • MW 2.20 • FW 1.55 • MB 2.44 • FB 1.81 • MMA 2.47 • FMA 1.56	SBP	**All β (SE), per ln µg/dL PbB: 1.07 (0.35); p<0.05***
			MW β (SE), per ln µg/dL PbB: 0.87 (0.53); p>0.05
			FW β (SE), per ln µg/dL PbB: 0.89 (0.55); p>0.05
			MB β (SE), per ln µg/dL PbB: 2.30 (0.71); p<0.05*
			FB β (SE), per ln µg/dL PbB: 2.40 (1.14); p<0.05*
			MMA β (SE), per ln µg/dL PbB: 0.10 (0.70); p>0.05
			FMA β (SE), per ln µg/dL PbB: -0.03 (0.64); p>0.05
		DBP	**All β (SE): 0.71 (0.27): p<0.05***
			MW β (SE): 0.90 (0.45): p<0.05*
			FW β (SE): 0.95 (0.38): p<0.05*
			MB β (SE): 2.75 (0.82); p<0.05*
			FB β (SE), per ln µg/dL PbB: 0.30 (0.81); p>0.05
			MMA β (SE), per ln µg/dL PbB: -1.34 (0.66); p<0.05*
			FMA β (SE), per ln µg/dL PbB: -0.74 (0.44); p>0.05

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Vupputuri et al. 2003[d] Cross-sectional study; n=14,952 total; n=5,360 MW; 5,188 FW; 2,104 MB; and 2,300 FB	Mean • MW 4.4 • FW 3.0 • MB 5.4 • FB 3.4	SBP	MW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.29 (-0.24, 0.83)
			FW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.34 (-0.49, 1.17)
			MB β, per 1 SD (3.3 µg/dL) increase of PbB: 0.82 (0.19, 1.44); p<0.05*
			FB β, per 1 SD (3.3 µg/dL) increase of PbB: 1.55 (0.47, 2.64); p<0.01*
		DBP	MW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.01 (-0.38, 0.40); p≥0.05
			FW β, per 1 SD (3.3 µg/dL) increase of PbB: -0.04 (-0.56, 0.47) p≥0.05
			MB β, per 1 SD (3.3 µg/dL) increase of PbB: 0.64 (0.08, 1.20); p<0.05*
			FB β, per 1 SD (3.3 µg/dL) increase of PbB: 1.07 (0.37, 1.77); p<0.01*
		Hypertension	MW OR: 1.04 (0.93, 1.16); p=0.47
			FW OR: 1.32 (1.14, 1.52) p<0.001*
			MB OR: 1.08 (0.99, 1.19); p=0.08
			FB OR: 1.39 (1.21, 1.61); p<0.001)*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Children and young adults[c]			
Gerr et al. 2002 Cross-sectional study; n=508 young adults (ages 19–29 years)	PbB mean associated with the following bone Pb concentrations: • <1 µg/g: 1.91 (1.58) • 1–5 µg/g: 2.31 (2.06) • 6–10 µg/g: 2.43 (2.36) • >10 µg/g: 3.15 (2.28)	SBP	**Increase (mmHg) associated with bone Pb >10 µg/g (SE): 4.26 (1.48); p=0.004***
		DBP	**Increase (mmHg) associated with bone Pb >10 µg/g (SE): 2.80 (1.25); p=0.03***
Gump et al. 2005 Prospective study; n=122 children assessed at 9 years of age	Cord PbB mean: 2.97	SBP	**β (SE), mmHg log µg/dL: 12.16 (4.96); p=0.016***
		DBP	β (SE), mmHg per log µg/dL: 8.45 (4.54); p=0.066
Gump et al. 2011 Cross-sectional study; n=140 children (ages 9–11 years)	Mean: 1.01 Quartiles: • Q1: 0.14–0.68 • Q2: 0.69–0.93 • Q3: 0.94–1.20 • Q4: 1.21–3.76	SBP	Under acute stress, p-trend over quartiles: 0.31
		DBP	Under acute stress, p-trend over quartiles: 0.29
		TPR	**Under acute stress, p-trend over quartiles: 0.03***

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Zhang et al. 2011 Prospective longitudinal study; n=457 mother-child pairs; children evaluated at ages 7–15 years	• Mean umbilical cord: 5.51 • Mean child concurrent: 2.96 • Median maternal postnatal tibia Pb (µg/g): 9.3	SBP	Maternal tibia Pb, boys, β, mmHg increased per maternal tibia Pb (13 µg/g): –0.34 (–1.98, 1.30)
			Maternal tibia Pb, girls, β mmHg increased per maternal tibia Pb (13 µg/g): 2.11 (0.69, 3.52); p=0.025*
		DBP	Maternal tibia Pb, boys, β, mmHg increased per maternal tibia Pb (13 µg/g): -0.83 (-2.05, 0.38)
			Maternal tibia Pb, girls, β, mmHg increased per maternal tibia Pb (13 µg/g): 1.60 (0.28, 2.91); p=0.007*
Blood pressure during pregnancy[c]			
Rothenberg et al. 2002b Longitudinal study; n=667 pregnant women	Mean: 1.9 Bone (calcaneous) Pb (µg/g) mean:10.7	SBP	Ln-PbB, β: -0.04 (-1.26, 1.18)
			Bone Pb, β: 0.70 (0.04, 1.36)*
		DBP	Ln-PbB, β: 0.20 (-0.78, 1.18)
			Bone Pb, β: 0.54 (0.01, 1.08)*
Wells et al. 2011 Cross-sectional study; n=285 pregnant women during labor	Umbilical cord PbB • mean: 0.66 • Quartiles: ○ Q1: <0.46 ○ Q2: 0.47–0.65 ○ Q3: 0.66–0.95 ○ Q4: 0.96–6.47	SBP	**Q4 versus Q1 increase in SBP in mmHg at admission: 6.87 (1.51, 12.21); p<0.05***
			Q4 versus Q4 maximum increase in SBP in mmHg: 7.72 (1.83, 13.60); p<0.05*
		DBP	**Q4 versus Q1 increase in DBP in mmHg at admission: 4.40 (0.21, 8.59); p<0.05***
			Q4 versus Q4 maximum increase in DBP in mmHg: Q4: 8.33 (1.14, 15.53); p<0.05*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Yazbeck et al. 2009 Cross-sectional study; n=971 pregnant women	Mean • Participants with PIH: 2.2 • Participants without PIH: 1.9	PIH	**OR for PIH for an increase of 1 log_{10} µg/dL in PbB; 3.29 (1.11, 9.74); p=0.03***

[a]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[b]If bone Pb is noted under results, study did not show associations between PbB and blood pressure parameters; however, results showed associations between bone Pb concentrations and increased blood pressure at concomitant PbB ≤10 µg/dL.
[c]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[d]Study population was from NHANES.
[e]Study population was from the Normative Aging Study.

B = black; CI = confidence interval; CL = confidence limit; DBP = diastolic blood pressure; F = female(s); M = male(s); MA = Mexican American; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PIH = pregnancy-induced hypertension; PP = pulse pressure; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; TPR = total peripheral resistance; W = white

The magnitude of effect on blood pressure observed in individual large-scale, cross-sectional studies is consistent with results of meta-analyses (see discussion above on *Characterization of Effects*). For example, Martin et al. (2006) reported that systolic and diastolic blood pressure increased by 0.99 (95% CI 0.47, 1.51; $p<0.01$) mmHg and 0.51 (95% CI 0.24, 0.79; $p<0.01$) mmHg, respectively, per 1 μg/dL increase in PbB.

Several studies have examined the relationship between PbB and blood pressure with study populations stratified according to gender, race, and/or age. For example, within study populations, positive associations were observed between PbB and systolic and diastolic blood pressure in men but not in women (Bushnik et al. 2014; Chu et al. 1999; Hense et al. 1993). However, other studies did not find differences between men and women (Bost et al. 1999; Scinicariello et al. 2011). Stratification by sex and age indicates additional differences between men and women. For example, Park et al. (2009b) reported a greater risk of hypertension in men >50 years of age (odds ratio [OR] 1.20; 95% CI 1.02, 1.41), but not in men <50 years of age (OR 0.98; 95% CI 0.80, 1.22), whereas in women, the opposite effect of age was observed, with a greater risk of hypertension in women <50 years of age (OR 1.23; 95% CI 1.04, 1.46) but not >50 years of age (OR 1.09; 95% CI 0.94, 1.26). Studies that stratify populations by race have found race differences in effect sizes on blood pressure. Large-scale cross-sectional studies based on data from NHANES have found larger effect sizes in non-Hispanic blacks and Mexican-Americans than in whites (Den Hond et al. 2002; Muntner et al. 2005; Scinicariello et al. 2011; Vupputuri et al. 2003). Cross-sectional studies based on data from NHANES have consistently shown elevations of systolic blood pressure in association with increasing PbB among black males and females, with less consistency in findings for other demographic groups or for diastolic blood pressure (Den Hond et al. 2002; Nash et al. 2003; Scinicariello et al. 2010, 2011; Vupputuri et al. 2003). Scinicariello et al. (2011) estimated increases in systolic blood pressure ranging from 1.07 to 2.4 per 1 ln increase in PbB (equivalent to approximately 0.7-1.66 per doubling of PbB). The largest effects sizes were observed in black males (2.3; SE 0.71 per ln PbB) and black females (2.4; SE 1.14). Den Hond et al. (2002) estimated the effect size for systolic blood pressure in black males and females to be 0.9 mmHg (95% CI 0.04, 1.8) and 1.2 mmHg (95% CI 0.4, 2.0) per doubling of PbB, respectively. Vupputuri et al. (2003) estimated the effect size for systolic blood pressure in black males and females to be 0.82 mmHg (95% CI 0.19, 1.44) and 1.55 mmHg (95% CI 0.47, 2.64) per 1 standard deviation (SD) increase (3.3 μg/dL) of PbB, respectively. As discussed above (see *Confounding Factors*), numerous co-variables and confounders affect studies of associations between PbB and blood pressure, complicating comparisons between studies.

Few studies have evaluated effects of chronic Pb exposure in children or young adults on blood pressure parameters at PbB at ≤10 μg/dL (Gerr et al. 2002; Gump et al. 2005, 2011; Zhang et al. 2011). Studies are briefly summarized in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 3. Population sizes in these studies are small (n=122–508) compared to studies in adults. Positive associations were observed between concurrent PbB and increased systolic and diastolic blood pressure in young adults (Gerr et al. 2002). Two prospective studies suggest that prenatal exposure to Pb is associated with increased blood pressure in childhood (Gump et al. 2005; Zhang et al. 2011). Umbilical cord PbB was positively associated with increased systolic, but not diastolic, blood pressure in children (Gump et al. 2005). Maternal postnatal bone Pb concentration was associated with increased systolic and diastolic blood pressure in girls, but not boys; however, no association was observed between umbilical cord PbB or patella Pb concentration and increased blood pressure (Zhang et al. 2011).

Effects of Pb on blood pressure and hypertension at PbB at ≤10 μg/dL have also been evaluated during pregnancy (Rothenberg et al. 2002b; Wells et al. 2011; Yazbeck et al. 2009). Studies are briefly summarized in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 3. Increases in systolic and diastolic blood pressure during pregnancy and labor were associated with PbB ≤10 μg/dL umbilical cord PbB, or bone Pb concentrations with concomitant PbB ≤10 μg/dL (Rothenberg et al. 2002b; Wells et al. 2011; Yazbeck et al. 2009). Pregnancy-induced hypertension has been positively associated with PbB ≤10 μg/dL (Yazbeck et al. 2009).

Atherosclerosis. Few studies have evaluated associations between PbB ≤10 μg/dL and atherosclerosis (Ari et al. 2011; Muntner et al. 2005; Navas-Acien et al. 2004). Studies are briefly summarized in Table 2-9, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 3. Ari et al. (2011) reported a positive correlation between PbB and intimal medial thickening of the greater carotid artery in non-diabetic hemodialysis patients at a concurrent PbB of 0.41 μg/dL. Peripheral artery disease was positively associated with PbB levels ≥2.47 μg/dL, with a positive trend across quartiles, in a study of a large NHANES 1999–2002 (age 18 years or older) population (Muntner et al. 2005), whereas analyses restricted to adult (≥40 years old) participants of NHANES 1999–2000 reported a positive trend for the risk of peripheral artery disease, although ORs for PbB quartiles (highest PbB quartile >2.90 μg/dL) were not associated with peripheral artery disease (Navas-Acien et al. 2004).

Table 2-9. Summary of Epidemiological Studies Evaluating Atherosclerosis at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Ari et al. 2011 Clinical study; n=50 adult male and female hemodialysis patients and 48 age- and sex-matched controls	Mean • Hemodialysis patients: 0.41 • Controls: 0.10	Greater carotid artery intima-media thickness	**β (SE), mm per µg/dL PbB: 0.101 (0.040); p=0.013***
Muntner et al. 2005[c] Cross-sectional study; n=9,961participants	Mean: 1.64 Quartiles: • Q1: <1.06 • Q2: 1.06–1.63 • Q3: 1.63–2.47 • Q4: ≥2.47	PAD	**OR for prevalence in Q4: 1.92 (1.02–3.61)*** **p-trend (across quartiles): <0.001**
Navas-Acien et al. 2004[c] Cross-sectional study; n=2,125 participants	Mean: 2.07 Quartiles: • Q1: <1.45 • Q2: 1.45–2.07 • Q3: 2.07–2.90 • Q4: >2.90	PAD	OR for prevalence in Q4: 2.88 (0.87, 9.47) **p-trend (across quartiles) for risk: 0.02***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Study population was from NHANES.

CI = confidence interval; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PAD = peripheral artery disease; SE = standard error

Heart disease. A series of studies conducted in men from the Normative Aging Study in the greater Boston, Massachusetts area evaluated associations between PbB ≤10 μg/dL and alterations in cardiac conduction and ischemic heart disease (Cheng et al. 1998; Eum et al. 2011; Jain et al. 2007; Park et al. 2009a). Studies are briefly summarized in Table 2-10, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 2. Studies show positive associations between bone Pb concentrations (at concomitant PbB ≤10 μg/dL) and changes to electrocardiograms (prolonged QT and QRS intervals) and atrioventricular conduction defect; however, no associations were observed between PbB and conduction abnormalities (Cheng et al. 1998; Eum et al. 2011; Park et al. 2009a). For ischemic heart disease, increased risks were associated with PbB and with tibia and patella Pb concentrations (Jain et al. 2007). A 1 SD increase in PbB was associated with a 1.27-fold increase in risk for ischemic heart disease.

Mortality due to cardiovascular disease. Mortality due to cardiovascular disease at PbB ≤10 μg/dL has been examined in large prospective and longitudinal studies, which provide mixed results. Studies are briefly summarized in Table 2-11, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 3. Three of these were conducted in large studies of men and women participating in NHANES (Aoki et al. 2016; Menke et al. 2006; Schober et al. 2006). Aoki et al. (2016) and Menke et al. (2006) observed positive associations of mortality due to cardiovascular disease, including myocardial infarction and stroke and at PbB ≤10 μg/dL, including positive trends for mortality with increasing PbB. In contrast, Schober et al. (2006) did not find increased cardiovascular mortality risk at PbB <10 μg/dL, although risk was increased at PbB ≥10 μg/dL and a positive trend for mortality was observed with increasing PbB. For PbB, no increased risk or positive trend for morality due to cardiovascular was observed in men from the Normative Aging Study (Weisskopf et al. 2009). In women, the risk of mortality due to coronary heart disease was increased at PbB ≥8 μg/dL compared to PbB <8 μg/dL (Khalil et al. 2009).

Table 2-10. Summary of Epidemiological Studies Evaluating Heart Disease at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Cheng et al. 1998[d] Longitudinal study; n=775 men (n=277 for men <65 years of age)	PbB mean: 5.8 Bone Pb, µg/g, mean (SD) • Tibia: 22.2 (13.4) • Patella: 30.8 (19.2)	QT interval	β, msec per 10-fold increase in PbB: -0.65 (-10.40, 9.10); p=0.90
			β, msec per 10-fold increase in tibia Pb: 5.03 (0.83, 9.22); p=0.02*
			β, msec per 10-fold increase in patella Pb: 3.00 (0.16, 5.84); p=0.04*
		QRS interval	β, msec per 1 unit increase in PbB: -3.49 (-10.72, 3.75); p=0.35
			β, msec per 1-fold increase in tibia Pb: 4.83 (1.83, 7.83); p<0.01*
			β, msec per 1-fold increase in patella Pb: 2.23 (0.10, 4.36); p=0.04*
		IVCD	**OR for a 10-fold increase in tibia Pb: 2.23 (1.28, 3.90); p<0.01***
Eum et al. 2011[d] Prospective longitudinal study; n=600 men	PbB baseline mean: 5.8 PbB Tertiles: • T1: <4 • T2: 4–6 • T3: >6 Tibia Pb (µg/g) baseline mean: 21.6 Tertiles: • T1: <16 • T2: 16–23 • T3: >23	QT interval	PbB OR for T3: 1.31 (0.69, 2.48); p-trend: 0.41
			Tibia OR for T3: 2.53 (1.22, 5.25)*; p-trend: 0.003*
		Atrioventricular conduction defect	PbB OR for T3: 0.52 (0.19, 1.45); p-trend: 0.16
			Tibia OR for T3: 0.23 (0.06, 0.87); **p-trend: 0.03**

Table 2-10. Summary of Epidemiological Studies Evaluating Heart Disease at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Jain et al. 2007[d] Longitudinal prospective study; n=837 men	PbB Baseline mean • Non-cases 6.2 • Cases 7.0 Patella Pb (µg/g) baseline mean • Non-cases 30.6 • Cases 36.8	Ischemic heart disease	**PbB β per 1 SD increase in PbB: 1.27 (1.01, 1.59)***
			PbB HR per 1 log increased in PbB: 1.45 (1.01, 2.06); p=0.05*
			Patella Pb HR per 1 log increased in bone Pb: 2.64 (1.09, 6.37); p=0.05*
Park et al. 2009a[d] Longitudinal prospective study; n=613 men	• PbB median (IQR): 5 (4–7) • Patella Pb (µg/dL), median (IQR): 26 (18–37) • Tibia Pb (µg/dL), median (IQR): 19 (14–27)	QT interval	PbB β for msec increase per IQR: 1.3 (-0.76, 3.36)
			Patella β for msec increase per IQR: 2.64 (0.13, 5.15)*
			Tibia β for msec increase per IQR: 2.85 (0.29, 5.40)*

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]If bone Pb is noted under results, study did not show associations between PbB and blood pressure parameters; however, results showed associations between bone Pb concentrations and increased blood pressure at concomitant PbB ≤10 µg/dL.
[d]Study population was from the Normative Aging Study.

CI = confidence interval; HR = hazard ratio; IQR = intraquartile range; IVCD = intraventricular conduction defect; OR = odds ratio; Pb = lead; SD = standard deviation

Table 2-11. Summary of Epidemiological Studies Evaluating Mortality due to Cardiovascular Disease at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Aoki et al. 2016[c] Prospective study; n=18,602	Mean: 1.73	Mortality due to cardiovascular disease	**RR, per 10-fold increase in PbB: 1.44 (1.05, 1.98)***
Khalil et al. 2009 Prospective study; n=533 women	Mean: 5.3	Mortality due to coronary heart disease	**PbB ≥8.0 compared to women with PbB <8.0. HR: 3.08 (1.23, 7.70); p=0.016***
Menke et al. 2006[c] Longitudinal study; n=13,946	Baseline mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.63	Mortality due to cardiovascular disease	**HR for T3 versus T1: 1.55 (1.08, 2.24)*; p-trend: 0.003***
		Mortality due to myocardial infarction	**HR for T3 versus T1: 1.89 (1.04, 3.43)*; p-trend: 0.007***
		Mortality due to stroke	**HR for T3 versus T1: 2.51 (1.20, 5.26)*; p-trend: 0.017***
			RR for T3 versus T1: 1.55 (1.16, 2.07)*; p-trend: <0.01*
Weisskopf et al. 2009[d] Longitudinal study; n=868 men	Mean: 5.6 Tertiles • T1: <4 • T2: 4–6 • T3: >6	Mortality due to cardiovascular disease	HR for T3 versus T1: 1.10 (0.67, 1.80); p-trend: 0.72

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]Study population was from NHANES.
[d]Study population was from the Normative Aging Study.

CI = confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; Pb = lead; RR = risk ratio

Associations Between Bone Pb and Cardiovascular Effects. Several studies have evaluated associations between bone Pb concentration and blood pressure and cardiac outcomes. Results provide evidence that long-term exposure to Pb produces adverse effects on the cardiovascular system.

Increased blood pressure and hypertension. Numerous studies show associations between bone Pb concentration and increased blood pressure and increased risk of hypertension (see Table 2-12). The most studied population is older men participating in the Normative Aging Study. Results consistently show positive associations between tibia Pb and systolic blood pressure (Cheng et al. 2001), pulse pressure (Jhun et al. 2015; Perlstein et al. 2007; Zhang et al. 2010), and risk of hypertension (Cheng et al. 2001; Elmarsafawy et al. 2006; Hu et al. 1996a; Peters et al. 2007). The association between bone Pb and elevated pulse pressure suggests that Pb may alter cardiovascular function through loss of arterial elasticity (Jhun et al. 2015; Perlstein et al. 2007; Zhang et al. 2010). Associations between patella Pb and blood pressure outcomes have been somewhat less consistent, with some studies showing positive associations (Hu et al. 1997; Jhun et al. 2015; Perlstein et al. 2007; Peters et al. 2007; Zhang et al. 2010) and other studies showing no associations (Cheng et al. 2001; Elmarsafawy et al. 2006). Other study populations examined include adults (Martin et al. 2006), young adults (Gerr et al. 2002), current and former Pb workers (Glenn et al. 2003; Lee et al. 2001), women (Korrick et al. 1999), pregnant women (Rothenberg et al. 2002b), and mother-child pairs (Zhang et al. 2001). Although study results are not consistent, positive associations between bone Pb and blood pressure and risk of hypertension have been reported. Navas-Acien et al. (2008) conducted a meta-analysis of 10 studies (see Table 2-12 for studies included in the analysis) to evaluate associations between tibia and patella Pb and blood pressure outcomes. Positive associations were observed between tibia Pb and systolic blood pressure and hypertension risk, but no associations were observed between tibia Pb and diastolic blood pressure or between patella Pb and systolic blood pressure, diastolic blood pressure, or hypertension risk.

Table 2-12. Associations Between Bone Pb and Blood Pressure Outcomes

		Blood pressure outcome			
Reference	Population	Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Cheng et al. 2001[a]	833 men[b]	↑ T 0 P	–	–	↑ T 0 P

Table 2-12. Associations Between Bone Pb and Blood Pressure Outcomes

Reference	Population	Blood pressure outcome			
		Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Elmarsafawy et al. 2006	471 men[b]	–	–	–	↑ T (at low dietary calcium) 0 P (at high dietary calcium)
Gerr et al. 2002[a]	508 young adults[c]	↑ T	↑ T	–	–
Glenn et al. 2003[a]	496 male Pb workers[d]	↑ T ↑ P	0 T 0 P	–	–
Glenn et al. 2006[a]	575 adult Pb workers[e]	↓ T	0 T	–	–
Hu et al. 1996a[a]	590	–	–	–	↑ T ↑ P
Jhun et al. 2015	727 men[b]	–	–	↑ T ↑ P	–
Korrick et al. 1999[a]	689 women (214 cases; 475 controls)[f]	–	–	–	0 T ↑ P
Lee et al. 2001[a]	924 adult Pb workers (789 cases; 135 controls[e]	↑ T	0 T	–	↑ T
Martin et al. 2006[a]	964 adults	0 T	0 T	–	↑ T
Perlstein et al. 2007	593 men[b]	–	–	↑ T ↑ P	–
Peters et al. 2007	512 men[b]	–	–	–	↑ T (with high stress) ↑ P (with high stress)
Rothenberg et al. 2002b[a]	1,006 pregnant women	–	–	–	↑ C (3rd trimester) 0 T (3rd trimester)
Schwartz et al. 2000c[a]	543 male Pb workers[d]	0 T	0 T	–	0 T
Weaver et al. 2008	652 Pb workers[e]	0 P	0 P	–	0 P
Zhang et al. 2010	612 men[b]	–	–	↑ T ↑ P	–

Table 2-12. Associations Between Bone Pb and Blood Pressure Outcomes

Reference	Population	Blood pressure outcome			
		Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Zhang et al. 2011	457 mother-child pairs[g]	↑ T (girls) 0 T (boys)	↑ T (girls) 0 T (boys)	–	–

[a]Included in the Navas-Acien et al. (2008) meta-analysis.
[b]Participants in the Normative Aging Study.
[c]19–29 years of age.
[d]Current and former Pb workers in the United States.
[e]Current and former Pb workers in South Korea.
[f]Nurses Health Study.
[g]Based on maternal bone Pb measurement.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; C = calcaneous bone; P = patella; Pb = lead; T = tibia

Cardiac function. Several studies evaluating associations between bone Pb and cardiac function, disease, and mortality were conducted in participants of the Normative Aging Study (see Table 2-13). For tibia Pb, positive associations have been observed for QT and QRS intervals (Cheng et al. 1998; Eum et al. 2011; Park et al. 2009a), atrioventricular and intraventricular block (Cheng et al. 1998), and ischemic heart disease (Jain et al. 2007). For patella Pb, positive associations were observed for QT and QRS intervals (Cheng et al. 1998; Park et al. 2009a). Both tibia Pb and patella Pb were positively associated with ischemic heart disease (Jain et al. 2007). However, no association was observed between tibia or patella Pb and all cardiovascular mortality or mortality due to ischemic heart disease (Weisskopf et al. 2009).

Mechanisms of Action. Several studies and recent reviews include discussions of mechanisms that may be involved in Pb-induced effects on cardiovascular function (Faramawai et al. 2015; Ghiasvand et al. 2013; Nawrot et al. 2002; Shiue et al. 2014; Weisskopf et al. 2009; Xu et al. 2015; Zota et al. 2013). Control of cardiovascular function is multi-factorial; therefore, numerous mechanisms are likely involved in Pb-induced cardiovascular effects. Specific mechanisms for cardiovascular effects include: impairment of renal function; effects on vascular smooth muscle, including constrictive effects and disruption of NO-induced vasodilatory actions; increase of sympathetic nervous system activity; and altered regulation of the renin-angiotensin-aldosterone axis and the renal kallikrein system. In addition, general mechanisms of toxicity of Pb, including oxidative stress, inflammation, and altered transport of ions across cellular membranes, also are likely to be involved (see Section 2.21).

Table 2-13. Associations Between Bone Pb and Cardiac Function, Disease, and Mortality

		Outcome		
Reference	Population	Function	Disease	Mortality
Cheng et al. 1998	775 men[a]	↑ T (QT and QRS intervals; AV block; IV block) ↑ P (QT and QRS intervals) 0 P (AV block; IV block)	–	–
Eum et al. 2011	600 men[a]	↑ T (QT and QRS intervals) 0 P (QT and QRS intervals)	–	–
Jain et al. 2007	837 men[a]	–	↑ T (IHD) ↑ P (IHD)	–
Park et al. 2006	413 men[a]	0 T (HRV with MetS) 0 T (HRV without MetS) ↑ P (HRV with MetS) 0 P (HRV without MetS)	–	–
Park et al. 2009a	613 men[a]	↑ T (QT interval) ↑ P (QT interval)	–	–
Weisskopf et al. 2009	868 men[a]	–	–	0 T (all cardiovascular or IHD deaths) 0 P (all cardiovascular or IHD deaths)

[a]Participants in the Normative Aging Study.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; AV = atrioventricular; HRV = heart rate variability; IHD = ischemic heart disease (defined as myocardial infarction or angina pectoris); IV = intraventricular; MetS = metabolic syndrome (three or more of the following: obesity, diabetes, hypertension, and dyslipidemia); P = patella; Pb = lead; T = tibia

2.7 GASTROINTESTINAL

Overview. Few epidemiological studies have evaluated gastrointestinal effects associated with chronic exposure to Pb. Almost all available studies were conducted in small numbers of workers with PbB >10 μg/dL, although one study included a group of workers with PbB ≤10 μg/dL. Study results consistently show gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea, and/or constipation) associated with PbB ranging from 8.04 μg/dL to approximately 100 μg/dL. As reviewed in

Section 2.2 (Acute Lead Toxicity), acute exposure to Pb is associated with gastrointestinal symptoms and intestinal paralysis.

The following gastrointestinal effects have been associated with PbB:

- ≤10 µg/dL:
  - Gastrointestinal symptoms (abdominal colic/discomfort).
- >10 µg/dL:
  - Gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea and/or constipation); corroborated in a few studies.

Measures of Exposure. Studies examining the association between gastrointestinal effects of Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors. Most epidemiological studies on gastrointestinal effects of Pb are survey or cross-sectional studies of small populations of workers. In general, studies did not consider confounding factors, such as age, diet, nutritional factors, alcohol use, and potential exposure to other occupational chemicals or limitations such as study design (cross-sectional and survey). Failure to account for possible confounders may overestimate associations between PbB and gastrointestinal effects.

Characterization of Effects. In contrast to the large number of epidemiological studies evaluating effects of Pb on other organ systems (e.g., neurological and cardiovascular outcomes), few epidemiological studies have investigated the gastrointestinal effects of chronic exposure to Pb (see Table 2-14). With the exception of a survey study conducted in 497 workers (Rosenman et al. 2003), studies were conducted in small worker populations (n=69–155). Increased gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea, and/or constipation) were observed in all studies. The lowest PbB associated with increased gastrointestinal symptoms showed an increased percentage of workers reporting abdominal colic and discomfort at a mean PbB of 8.04 µg/dL, compared to controls (PbB 5.76 µg/dL) (Kuruvilla et al. 2006). For example, 18.9% of painters reported abdominal colic compared to 0 in the control group.

Effect at Blood Pb Levels ≤10 µg/dL. See discussion above on Kuruvilla et al. (2006).

Table 2-14. Summary of Studies Evaluating Gastrointestinal Symptoms Associated with Chronic Exposure to Lead (Pb)

Reference and study population	PbB (µg/dL)	Outcomes evaluated[a]	Effects[b]
Awad el Karin 1986 Cross-sectional study; n=92 exposed; 40 controls	Range of means (by job category): 48.1–80.7 Controls mean: 21.2	Abdominal colic	• Exposed (% reporting symptom) 41.3; **exposed versus control p=0.01*** • Control (% reporting symptom): 7.5
		Constipation	• Exposed (% reporting symptom) 41.4; **exposed versus control p=0.01*** • Control (% reporting symptom): 10.0
Baker et al. 1979 Survey study; n=160 Pb workers	Range of means (by job category): 41.8–87.2	Gastrointestinal symptoms	• **Mean PbB at which symptoms are present: 101.24 µg/dL (p<0.01)*** • PbB, symptom absent: 65.98 µg/dL
		Abdominal pain	• **PbB, symptoms present: 100.77 µg/dL (p<0.01)*** • PbB, symptom absent: 68.25 µg/dL
Kuruvilla et al. 2006 Cross-sectional study; n=155; exposed workers: n=105 (52 battery workers; 53 painters); controls: n=50	Mean • Battery workers:42.40 • Painters: 8.04 • Controls: 5.76	Abdominal colic	• **Battery workers (% reporting symptom): 17.3; p<0.01** • **Painters (% reporting symptom):18.9; p<0.01*** • Controls (% reporting symptom): 0
		Abdominal discomfort	• **Battery workers (% reporting symptom): 19.2; p<0.01*** • **Painters (% reporting symptom): 26.4; p<0.001*** • Controls (% reporting symptom): 2
		Vomiting	• Battery workers (% reporting symptom): 1.9 • Painters (% reporting symptom): 1.9 • Controls (% reporting symptom): 0
		Constipation	• Battery workers (% reporting symptom): 0 • Painters (% reporting symptom): 1.9 • Controls (% reporting symptom): 2

Table 2-14. Summary of Studies Evaluating Gastrointestinal Symptoms Associated with Chronic Exposure to Lead (Pb)

Reference and study population	PbB (µg/dL)	Outcomes evaluated[a]	Effects[b]
Matte et al. 1989 Survey study; n=69 (46 manufacturing and 23 battery repair workers)	• Mean: not reported • Workers stratified by PbB <60 and ≥60	Nausea	• PbB <60 (% reporting symptom): 7 • PbB ≥60 (% reporting symptom): 14 • PR (95% CI): 2.0 (0.5, 7.9)
		Abdominal pain	• PbB <60 (% reporting symptom): 12 • PbB ≥60 (% reporting symptom): 18 • PR (95% CI): 1.5 (0.5, 4.6)
Rosenman et al. 2003 Survey study; n=497 workers	• Range 10–70 • Stratification by PbB: ○ 10–24 (n=139) ○ 25–29 (n=98) ○ 30–39 (n=171) ○ 40–49 (n=58) ○ 50–59 (n=22) ○ ≥60 (n=9)	Abdominal pain	AdjOR (95% CI) for PbB: • 10–24: 1 (reference) • 25–29: 0.62 (0.28, 1,37) • 30–39: 0.98 (0.53, 1.82) • **40–49: 2.15 (1.03, 4.49)*** • 50–59: 1.54 (0.52, 5.23) • ≥60: NR

[a]Gastrointestinal symptoms include abdominal colic, nausea, vomiting, diarrhea, and/or constipation.
[b]Asterisk and **bold** indicate association with Pb.

AdjOR = adjusted odds ratio (adjusted by age, ethnicity group, company screening, and smoking status); CI = confidence interval; NR = not reported; PbB = blood lead concentration; PR: prevalence ratio